

BRUCELLOSIS

A Public Health Problem

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Foreword

The writer has selected the subject, "Brucellosis, a public health problem", as a dissertation for two reasons:

Firstly, the subject has great scientific interest for the student of bacteriology and pathology in particular, and in general for the epidemiologist and epizootologist as well as for the practitioners of human and veterinary medicine. It is of immediate interest to the considerable number who are infected and of more than passing significance to the general public who are constantly or occasionally exposed to a number of sources of infection and who have been trained, in the United States at least, to place reliance in governmental protection against diseases of this nature. It is of especial interest to the owners of susceptible livestock and to all those who are connected with the industries that handle animals and animal products. Their exposure to infection is greatest and their economic stake is tremendous whether they do nothing to control the disease or whether they undertake to control it on their own initiative or under public or legal pressure, with or without financial or technical governmental aid. Finally it is of political interest since history teaches us that problems of this kind are thrust upon or are grasped by those in political power in the various units of American government and it is, therefore, desirable that political action be wise. The investment in governmental disease control—especially animal disease control—campaigns has been in similar cases enormous, and the interference with private practices and affairs has resulted in much litigation and bad feeling regardless of the fact that the end, both in public health and economic welfare, has justified the means.

Secondly, the writer should possess some qualifications for a synthetic study of the problem. He has worked with *Brucella* diseases in the laboratory, in the field, and in an advisory and administrative capacity for a quarter of a century. Except for a few isolated discoveries, of momentous importance nevertheless, all of our scientific and hence, practical, knowledge of the disease has been acquired in this period. The writer selected the subject of bovine infectious abortion, one of the brucelloses, as a subject for major research when the Adams fund was first made available for the support of fundamental investigations in agriculture at the Michigan Agricultural Experiment Station. He thought at the time that it would be a problem to occupy an investigator's closest attention for at least 25 years. It is now apparent that the magnitude of the undertaking was greatly underestimated. A considerable band of investigators has, in the

past quarter century, not solved the problem, but only demonstrated that it has many ramifications and that there are hopeful approaches.

The writer did not get very far with his own unaided researches and he did not get very far into the subject until it became apparent that it would be necessary to build up a competent staff for an effective attack. At the present time there is at Michigan State College under his immediate or remote direction, a fairly complete and well balanced program for the study of brucellosis in all its aspects. In the Department of Bacteriology and Hygiene, there is (1) the Central *Brucella* Station, supported jointly by the Experiment Station, the National Research Council, and other private agencies,* and the U. S. Department of Agriculture. Its staff comprises four full-time employees and two graduate student assistants. Its program is both extensive and intensive. There is also (2) a project designed to test the effects and the effectiveness of an avirulent vaccine as a control measure. In the Department of Animal Pathology, investigations are in progress independently and in cooperation with the Department of Bacteriology and Hygiene, (1) especially along the lines of histo-pathology and (2) a field project designed to produce abortion-free herds of cattle which will in turn be officially accredited by the State Department of Agriculture.

Another stimulus to a deep interest in brucellosis is the very considerable number of visitors to our laboratory. They include students of the subject from all parts of the United States and Canada, from Mexico, Chili, British West Africa, Italy, France, England, and Scotland.

The importance of *Brucella* and brucellosis studies may be inferred from the following quotations which express the mature judgment of two authorities.

In the DeLamar lecture delivered October 30, 1928, before the Johns Hopkins University School of Hygiene, Theobald Smith made the following introductory remarks: "It is somewhat hazardous to deliver a formal lecture on a subject in which we are just beginning to realize the importance of accurate data and in which a fair number of questions can be asked and problems formulated, but no definite conclusions drawn. As in nearly all somewhat unexpected developments in science, the new problem of undulant fever in populations not using goat's milk seemed at first simple. The cow was regarded as the source of the infection owing to the wide dissemination of the bovine disease. The problem has grown more obscure and complex with the publication of fresh cases and the more thorough study of the organisms obtainable from them. Hasty conclusions in this as in other fields of public health may do no damage as long as the problem remains in the stage of discussion. The results are more serious when hasty legislation results or new rulings under existing law are promptly invoked. Moreover such action may tend to discourage or stifle further necessary research".

Charles Nicolle† one of the most distinguished students of undulant fever, has made this prediction concerning the disease:

"Mediterranean fever is in the course of evolution, and is tending to become chronic. It is a malady which, on account of its manifestations and chronicity, will become one of the commonest and most stubborn diseases Mediterranean fever is a disease of the future."

*Commonwealth Fund, American Med. Assoc., Certified Milk Producers Assoc., and Detroit Edison Co. Dr. C. P. Beattie, Edinburgh, Scotland, traveling Fellow, Rockefeller Foundation, has rendered valuable assistance (winter 1932-1933).

†Quoted by Gentry, p. 864, Oxford Loose Leaf Medicine, 1930. Also by Roger, Henri (1932): *La neuromélicococcie*. Presse medicale, 40, p. 378.

I. INTRODUCTION

Definitions and Nomenclature—The disease. Brucellosis* (brucelliasis) is the name recently given to a disease formerly referred to as Malta fever, Mediterranean fever or undulant fever. The name, brucellosis, is based on one of the commonly used generic names of a group of bacteria that produce disease in man, and in goats, cattle and other domesticated animals. The disease was originally observed and studied especially in man and goats in Mediterranean countries, more particularly on the Maltese Islands,—Malta, Gozo, Comino, and Cominotto, the two latter being practically uninhabited. The Maltese object, naturally, to the unfavorable advertising that results from the term Malta fever, so much so that the League of Nations Health organization uses the name undulant fever in the official list of diseases. The designation, Mediterranean fever, is objectionable as are geographical descriptive names of diseases in general. Brucelloses are world wide in distribution and occurrence. Undulant fever is objectionable except as a name for certain types of human brucellosis, since the descriptive adjective is usually not applicable to the animal brucelloses and not always to human brucellosis.

Hughes (1) defines undulant fever as “an endemic pyrexial disease, occasionally prevailing as an epidemic, having a long and indefinite duration, an irregular course with an almost invariable tendency to undulatory pyrexial relapses. It is usually characterized by constipation, profuse perspirations, and is accompanied by swelling and effusion of the joints and other rheumatoid symptoms. After death, the spleen is found to be enlarged and often softened, many of the organs congested, but the Peyer's glands neither enlarged nor ulcerated, nor is ulceration present in other parts of the small intestine. There is a constant occurrence in certain tissues of a definite species of micro-organisms.” (Page 1)

Bang's disease is the common form of brucellosis found in cattle. It derives its name from the Danish veterinarian† whose work will be referred to later. This disease is frequently called infectious, contagious, or epizootic abortion. While the descriptive adjectives are not objectionable, the noun is very misleading, since abortion is not a sufficiently constant manifestation of brucellosis in cattle to warrant the use of the word in designating the disease.

The Bacillus—*Micrococcus melitensis* is the name given by Hughes (1) in 1893 to the bacillus seen in splenic sections by Bruce (2) in 1886, and isolated by the latter from human cases of fever on the Island of Malta in 1887.‡

*Brucellosis is preferable to brucelliasis since the ending-*osis* is more commonly employed in connection with designations of diseases due to vegetable pathogens, for example mycosis, blastomycosis, aspergillosis, bacillosis, spirochetosis, tuberculosis and many others; while-*iasis* is the more common ending for words designating diseases due to an animal pathogen, for example, ascariasis, filariasis, trypanosomiasis, amebiasis, myiasis. There are, of course, glaring exceptions such as, coccidiosis, proplasmiasis, etc.

(1) Numbers refer to references listed on pages 107 to 115.

†Note editorial in Am. Jr. Pub. Health, Vol. XXIII, 1933, pp. 48-49.

‡Bruce seems to have been the first to name the microbe, *Micrococcus melitensis*. Bruce, D. (1893): Une nouvelle forme de fièvre rencontrée sur les bords de la Méditerranée. Ann. de l'Inst. Past., Vol. 7, p. 289.

Bacillus abortus is the name of the bacillus isolated by Bang and Stribolt (3) (1897) from the placenta of a cow and her fetus. The cow was slaughtered at the time of an approaching abortion. This short non-motile rod has been called *Bacterium abortus* and, by Bergey's Manual of Determinative Bacteriology (4), *Alkaligenes abortus*. The generic name, *Brucella*, is particularly more acceptable than is *Alkaligenes* which is based on their property of producing alkali in suitable media.

When Evans (5) (1918) made a comparative study of *Micrococcus melitensis*, *Bacterium abortus*, and *Bacterium bronchisepticus*, she concluded that they are related morphologically, culturally, biochemically, and serologically. However, she did not establish the identity of the first two.

Already in 1914, Traum (6) had isolated from an aborted pig fetus a bacillus which he considered to be *Bacterium abortus*; and, in 1916, Good and Smith (7) reported on this bacillus as the etiological factor in the production of infectious abortion of swine.

Huddleson's (8) studies on the *Brucella* group resulted in his conclusion that there are three distinct species, *Br. melitensis* of the goat, *Br. abortus* of cattle, and *Br. suis* of swine, with other hosts aside from the primary host in each case. Hardy (9) prefers to use the single designation, *Brucella melitensis*, with varieties under this species rather than distinct species, thus:

Brucella melitensis (Bruce) to be *Brucella melitensis* var. *melitensis*

Brucella abortus (Bang) to be *Brucella melitensis* var. *abortus*.

Brucella suis (Huddleson) to be *Brucella melitensis* var. *suis*.

The writer prefers the simpler classification of Huddleson and believes that there are sufficient differences between the varieties of Hardy to warrant species designations.

Historical

Malta Fever of Goats and Man—Surgeon-Captain Hughes (1) (1897) summarized our knowledge of "Mediterranean, Malta or Undulant Fever" in his interesting book of that title and prepared a bibliography (see Bibliographies p. 115) down to that date. In his preface, he states that: "When the writer arrived in Malta towards the end of the year 1890, for six years' tour of service (British army) in that place, he found that his medical work would chiefly consist, during the greater part of the year, of treating a fever about which no two medical officers appeared to agree, respecting its cause, treatment, or even name." Surgeon-Captain Hughes contracted the fever as did his wife and two sisters and as did many British soldiers stationed in the Mediterranean, especially on the Island of Malta.

He gives an extensive synonymy for the disease based on its supposed resemblance to typhoid or malaria, its remittent character, the occurrence of gastric derangements or other symptoms, its lengthened course and indefinite duration, its geographical prevalence, and its supposed origin. He gives numerous and rather convincing reasons for the name "undulant fever". In addition to Mediterranean countries, Hughes gives evidence of the possibility of the existence of undulant fever in China and India and discusses the occurrence of certain types of fever in America. "These cases have been termed 'typho-malarial fever' by Woodward (1876), Maurel (1879) Bartlett (1881), and Webb (1883). In the valley of the Mississippi, they were called 'malarial continued fever' by Maury (1881), who has published some interesting temperature charts". Hughes' bibliography, after referring to suggestive descriptions in the epidemics of Hip-

pocrates (460-357 B. C.) (Adams translation) dates back to 1709 and includes references for the year 1897.

"The accurate history of undulant fever commences from the year 1859, when Marston wrote the first description of the fever as a distinct disease" (Army Medical Report 1863). "A careful study, however, of the literature of the fevers of the Mediterranean prior to 1859, leads one to believe that this particular fever must have prevailed in many of the towns on its coasts during the last century if not at an earlier period" (1).

During the eighteenth century, according to Hughes, Howard (1786), Cleghorn (1751), and others describe fevers that were probably undulant fever. During the early nineteenth century, there are more numerous references to such fevers. Thus, Hennen (1816-1825) states, "The mortality from fevers amongst the native population of Malta, from 1818 to 1823, was 1 in 66.71 of the total population (96,404), for the six year period being a tenth of the total mortality from all causes. If we study the official parliamentary statistics of sickness among the troops serving in the Mediterranean, for the years from 1817 to 1840, we find much the same class of fevers prevailing at the present day, though greater in amount. Common continued fevers (undulant fever) was the cause of by far the greater proportion of deaths from this class of disease. (1)

"In 1879, Surgeon-Major Veale, in the Army Medical Report, published a paper which with those of Marston and Bruce, may be termed one of the three classics concerning undulant fever" (1). Reference has already been made to Bruce's discovery of the micrococcus of undulant fever.

In 1891, Hughes (1) began to work with the bacteriology of undulant fever as well as with its predisposing causes, method of propagation and dissemination, age and sex distribution, incubation period, seasonal prevalence, influences of rainfall and temperature, immunity from subsequent attacks, and statistical aspects. One significant conclusion was, "It does not appear to be contagious directly from man to man". However he did not demonstrate how it was transmitted.

He also studied thoroughly symptomatology and differential diagnosis, prognosis, mortality, and both gross and microscopic morbid anatomy. Attention has already been called to the discovery of the *Micrococcus melitensis* by Bruce and the naming of the microbe by himself and by Hughes.

The commission appointed by the British Admiralty, the War Office, and the Civil Government of Malta began its investigation of Mediterranean fever in 1904. The work was under the supervision of an advisory committee of the Royal Society and was in more immediate charge of a sub-committee of the Tropical Disease Committee consisting of Colonel Bruce, Fleet-Surgeon Bassett-Smith, Drs. Klein, C. J. Martin, and Sidney Martin. The sub-committee appointed Major Horrocks, Staff-Surgeon Shaw, and Dr. Zammit, Board of Health of Malta, as members of the Commission and Colonel Bruce to assist them in commencing the work. Dr. Johnstone was lent by the Local Government Board to assist the commission. Staff-Surgeon Gilmour of Malta also assisted.

The results of the commission's researches began to appear as early as July 14, 1904. Exhaustive studies* were made on the cultivation, viability,

*In the Obituary of Sir David Bruce, Transactions Royal Soc. of Trop. Med. and Hyg. V. 25, pp. 305-312, 1932, A. E. Hamerton states that the researches of the Malta Fever Commission of 1904 and 1905 "laid the foundation of perhaps the most brilliant piece of team work in the annals of preventive medicine," namely the researches of the Malta Fever Commission of 1904 and 1905.

who drank little of the milk and two German engineers, who appear to have boiled it, escaped.

There is no history of the disease appearing at the quarantine station in Antwerp or on the S. S. "St. Andrew". A woman at the quarantine station in America developed the disease.

The Report of the work of the Commission for the Summer of 1906 concludes, (Part VI, p. 130)

(a) "The most common method of infection is by the ingestion of infective articles of food—mainly milk.

(b) "The next common path of infection is by subcutaneous inoculation during the handling of infective material—usually milk.

(c) "More rarely infection may occur as a result of contagion, or, possibly, through convection by means of blood-sucking insects."

Infectious Abortion of Cattle—It is necessary to discuss Bang's disease, *brucellosis bovis*, in connection with undulant fever, *brucellosis hominis*, for reasons that will be made clearer. The observation is pertinent at this time that, had students of either undulant fever or infectious abortion of cattle had any suspicion of a relationship between the two diseases, it would have served well the students of the latter disease to have thoroughly studied the work of Hughes and the Reports of the Commission for the investigation of Mediterranean fever. It is with mixed emotions that one contemplates what progress might have been made and what time certainly would have been saved if the study of infectious abortion of cattle in northern Europe and America a quarter of a century ago had begun with these great works as guides.

In 1897, Bang (3) published the results of his studies on epizootic abortion of cattle in Denmark. He concluded that the disease is a specific uterine catarrh caused by a definite species of bacterium which he isolated in pure culture at the time of slaughter from the affected tissues of a cow that was about to abort. This bacterium, Bang's bacillus, *Bacterium abortus*, etc., was observed to have, according to Bang's incorrect interpretation, peculiar oxygen requirements. Bang's work certainly did not receive the attention it deserved either in Europe or America for over a decade.

In 1905, the British Board of Agriculture and Fisheries (26) appointed a Committee "to inquire, by means of experimental investigation and otherwise, into the pathology and etiology of epizootic abortion, and to consider whether any, and if so, what, preventive and remedial measures may with advantage be adopted with respect to the disease." The personnel of the Committee was: Sir Edward Strachey, The Rev. Dr. John Gillespie, Professor John McFadyean (Royal Veterinary College), Chairman, Mr. William Hunting, Dr. George H. Falkiner Nuttall, (Cambridge), and Mr. Stewart Stockman, Chief Veterinary Officer of the Board of Agriculture and Fisheries. They made a report that gave evidence of careful study of the disease, but, of course, no mention was made of undulant fever, nor was there any hint of a menace to man from the bovine brucellosis.

The investigations of this disease in both Europe and America from this date were numerous, but none were of significance to us until 1918, when Evans (5) published her paper on "A comparison of *Bacterium abortus*

with *Bacterium bronchisepticus* and with the organism which causes Malta Fever". She concluded,*

"It is only with great difficulty that *Bact. melitensis* can be distinguished from *Bact. abortus*. They are alike morphologically, and no difference could be found in their biochemical reactions. The two organisms produced the same results when inoculated into pregnant guinea pigs. The only distinction between the two organisms in cultural characteristics was a more intense brown pigmentation by *Bact. melitensis*—an insignificant characteristic, which does not appear until after the cultures have been incubated for a week or more. This distinction can be made only when cultures of the two species which have been incubated for the same length of time can be compared. The agglutination reactions in *Bact. abortus* antiserum do not distinguish the two organisms; and the agglutination reactions in *Bact. melitensis* antiserum can distinguish *Bact. abortus* and *Bact. melitensis* only when the agglutinating strength of the serum for both species is known.

"The fact that *Bact. abortus* and *Bact. melitensis* are serologically so closely related explains Kennedy's† discovery that the milk and the blood serum of a considerable percentage of cows in London contained agglutinins for the Malta fever organism in high dilution. This author was unable to explain his findings, but suggested that agglutination of the Malta fever organism by cows' milk was not necessarily specific, or else that the reaction was indicative of infection with the organism in question—the latter alternative being an explanation too alarming to be acceptable, although he states that he has heard of two cases of undulant fever in people who have never been out of England, and he thinks it possible that there are other cases undiagnosed.

"The very close relationship between *Bact. abortus* and an organism pathogenic to human beings adds new interest to the subject of the possible pathogenicity of *Bact. abortus* to human subjects. Considering the close relationship between the two organisms, and the reported frequency of virulent strains of *Bact. abortus* in cows' milk, it would seem remarkable that we do not have a disease resembling Malta fever prevalent in this country. A possible explanation can be offered. The data presented in the third paper of this series indicates that although there may be numerous abortus-like bacteria in the milk of cows which have aborted, the actual number of virulent bacteria which persist in the milk is not great, or in all probability it is negligible in many cases in which the milk and blood serum contain agglutinins. But the work of the British Commission indicates that *Bact. melitensis* is very abundant in the milk of infected goats, for those investigators were able by cultural methods to demonstrate the organism in the milk of 10 per cent of the goats of Malta. Since infection is dependent on the amount of infectious material, it may be that this difference in the number of bacteria in the milk of the two species of animals may account for our freedom from disease when cow's milk containing *Bact. abortus* is consumed. On the other hand, are we sure that cases of glandular disease, or cases of abortion, or possibly diseases of the respiratory tract, may not sometimes occur among human subjects in this country as a result of drinking raw cows' milk? It is certain that the agglutination tests, which have been relied on for the diagnosis of Malta fever, have not proved per se whether the infections were due to *Bact. melitensis* or *Bact. abortus*.

Summary

"*Bact. abortus* and *Bact. bronchisepticus* are related. They resemble each other morphologically, culturally, biochemically and serologically. *Bact. bronchisepticus* can be easily distinguished from *Bact. abortus*, however, by its motility, by its more rapid and abundant growth in all artificial media, by its more intense alkaline reactions, and by its agglutination in *Bact. abortus* immune serum only in low dilutions.

"The organism which causes Malta fever is unquestionably a rod form and should be called *Bact. melitensis*.

*According to deKruif, Paul (1932): *Men against death*, Harcourt, Brace and Co., p. 151, this work was suggested by Dr. A. Eichhorn of the Federal Bureau of Animal Industry.

In a thesis presented to the Faculty of Medicine and Pharmacy of Lyon for the degree of Docteur Vétérinaire entitled *Contribution à l'Etude des Rapports existant entre la fièvre ondulante de l'homme et l'avortement épidémiologique des animaux*, 1928, this statement is found on page 17: "Dès 1908, Panisset (11) avait déjà attiré l'attention sur les rapports très étroits qu'entretenaient les deux germes * * *". The reference 11 is: "Panisset.—Une remarquable parenté bactériologique: identité du microbe de la fièvre de Malte et de l'agent de l'avortement épidémiologique (Biologie médicale, 1910, p. 117)". The writer has been unable to consult the original so cannot make any statement relative to any claim that Panisset may have to priority in calling attention to the relation between *Br. melitensis* and *Br. abortus*.

†*Jour. of the Royal Army Med. Corps*, 1914, 22, p. 9.

acquired from cows affected with true *melitensis* infection rather than *abortus* infection. He and his associates have succeeded in making blood cultures from man using the peculiar gas requirements of *abortus*. Kristensen (36), of Denmark, could isolate *Brucella* from only 23 of 500 cases (5 per cent), while blood cultures are possible in a majority of cases of brucellosis *melitensis*. Favilli (28), of Florence, writes that, since cattle seem to be the cause of undulant fever of man in England and Germany, where *melitensis* infection is (supposed to be) absent, it seems that Bang's bacillus must be considered the cause of the disease in those countries.

At the Eleventh International Veterinary Congress, Gofton (37) reported that: "Dalrymple-Champneys in a report on the subject prepared on the instructions of the ministry of Health and issued in 1929, states that 'only fourteen well authenticated cases of undulant fever originating in England have been found in the literature, and in only three of these was there very good evidence of the source of infection, in one case goat's milk and in the other two cases cow's milk, the organism in each case being probably of the *abortus* variety'. Having regard to the widespread prevalence of bovine contagious abortion in Great Britain and to the large quantities of milk which are consumed in the raw state, it is clear that abundant opportunities occur for human infection with *Br. abortus*, but existing evidence of such infection is negligible".

Kathe (38) reports human cases due to *Bacterium abortus* (Bang) as being frequent in Silesia.

Zwick (39) states that the present state of our knowledge indicates that contagious abortion in the sheep and pig is not very widespread and of far less importance than is the bovine disease. A. Uranov and B. Bohl (40) observed brucellosis in the large English breeds of pigs in two districts of Northern Caucasus in 1929. Stafseth reports to me personally that he observed severe outbreaks of the disease in swine in Hungary.

In the United States brucellosis of caprine origin has occurred as a result of the importation of infected goats, but only in isolated cases. It is a potential menace in the southwestern states bordering on Mexico, and it may spread to any section that develops an interest in the milk goat industry either as a result of true *melitensis* infection or as a result of goats becoming infected by other species of *Brucella*. At the present time, and probably permanently, the goat is the least serious of the known main reservoirs of infection for man in the United States and Canada.

The problem of brucellosis caused by *abortus* is serious. The main reservoir of *abortus* is the bovine, but it has been found also in the sheep, goat, horse, and domestic fowls. Cattle are a source of human infection both as a result of human contact with infected animals and through the ingestion of raw dairy products. Infectious abortion of cattle is a very widespread disease in the United States. It is considered to be the most serious cattle disease with which animal husbandry has to contend.

Brucellosis of swine has received less attention than has the corresponding disease in goats and cattle. It is known to be very prevalent in Iowa and to exist in other states of the Middle West. Contact between swineherds and affected hogs and between butchers and pork products makes exposure certain and infection not infrequently results. Brucellosis of poultry and horses is known to exist in the United States and in Europe, but the available evidence sheds little or no light on its role as a factor in the problem as a whole.

Brucellosis in Other Countries

Morales-Otero (33) has studied brucellosis in Porto Rico. Bevan (41) of Rhodesia was the first to report a suspected case of human brucellosis of bovine origin. As early as 1921, Bevan spoke before the Southern Rhodesia Veterinary Association as follows: "Certain cases presenting symptoms resembling Undulant fever have occurred in Southern Rhodesia in men who, as far as is known, have not obtained infection from goats, but have resided on farms where animals are or have been infected with infectious abortion.

"It is suggested that these cases are suffering from an infection caused by *B. abortus* of cattle. It is also suggested that human females may contract infectious abortion through the ingestion of the organism in milk and dairy products from infected cows. While circumstantial evidence points to the infection of man by the *B. abortus* of Bang and scientific tests up to a point support this suspicion, the final proof is not yet available. If infectious abortion of cattle is essentially a bovine disease a grave responsibility attaches to the Veterinary Department; and if the disease is communicable to man, a hearty cooperation between the medical and the veterinary profession is necessary in dealing with it".

Later (1925) Bevan (42) stated that, in areas where undulant fever occurs in Rhodesia, "the strains of infection are probably of 'native' and South African origin". No patients are found in certain districts where infectious abortion exists in cattle.

Conversations with visitors from Mexico, Cuba, Chili, British East Africa, and other countries to our laboratory, and correspondence concerning the problem clearly indicate that *Brucella* disease occurs in all parts of the civilized world especially in cattle. Its occurrence in man is a matter concerning which definite information is fragmentary. There is reason to believe that no patients are found in certain districts where infectious abortion exists in cattle; and it is certain that cases have suddenly appeared apparently as a consequence of an effort to locate cases by means of scientific methods of diagnosis such as the serum agglutination test.

Recently Jordan and McBroom (43) reported brucellosis in dairy cattle in the Canal Zone, but they state that no cases of undulant fever in man, traceable to cattle, have yet been recorded in the zone.

Statistical Evidence

Cattle Abortion

Cotton (44) states "No systematic survey to determine the incidence of the disease (infectious abortion of cattle) has been made, but much blood-testing has been done in a number of States, which indicates that the proportion of infected herds in some localities may exceed 50 per cent and the number of reacting cattle in such herds may average about 20 per cent. The losses (in the United States) caused by the malady have been estimated to exceed \$50,000,000 per annum and may be greatly in excess of this figure". Cotton further states, "It is probable that the greatest cattle plague in the United States is infectious abortion. The disease in swine has appeared in the principal hog-raising States, but does not yet cause sufficient economic loss for alarm. However, it has attracted considerable

attention of late because it has been found that infectious abortion of both swine and cattle is of significance to human health. Abortion in sheep has not been reported as causing severe losses except in few localities".

No accurate and reliable statistical records are available on the subject of abortion disease in cattle, swine or other livestock in this country. Only a campaign of eradication or preliminary surveys based on the use of the agglutination diagnostic test and covering representative areas will yield satisfactory records.

In 1917, Eichhorn and Potter (45) wrote, "Contagious abortion of cows, it was estimated a few years ago caused an annual loss (in the U. S.) of \$20,000,000, but since that time it has continued to spread rapidly and widely throughout the country".

Later in the same year, Hayes (46) wrote, "With the exception of tuberculosis no disease of cattle is of so much economic importance in California at this time as infectious abortion".

The Kansas Agricultural Experiment Station (47) went on record in 1918 as follows, "To the cattle industry of Kansas, this disease (contagious abortion of cattle) is a serious and ever increasing menace. Our breeding herds of beef cattle in pasture and on range have been hard hit, in many cases the losses amounting to nearly the entire calf crop. The dairy herds have likewise suffered".

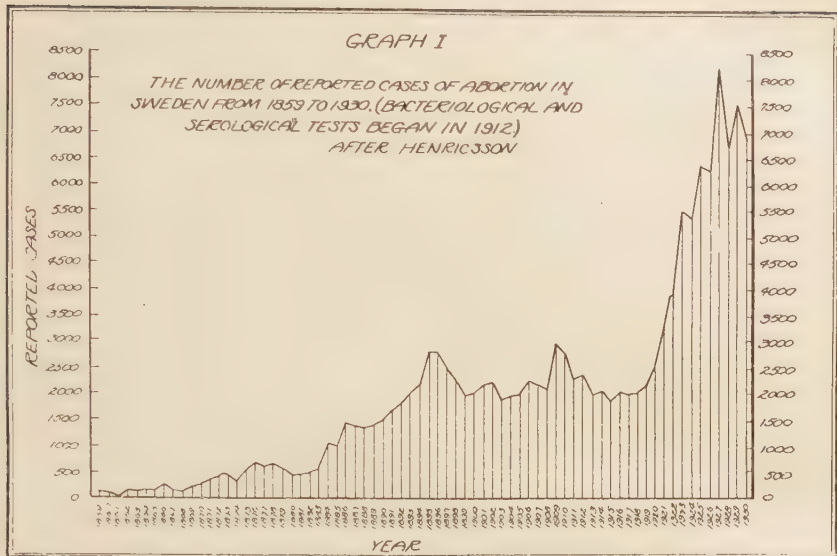
In 1924, Hadley (48) wrote as follows, "It is estimated that about eight per cent out of all milk cows abort each year. Assuming that the resulting loss is \$25.00 per head, which certainly seems to be a reasonable estimate, considering the price of feed and milk, the total loss for Wisconsin can be computed if the number of cows is known. The assessors' reports for 1920 give the cow population of Wisconsin at 1,828,000 head. On this basis the annual loss would be about \$3,631,000".

In 1927, Carpenter and Baker (49) stated, "An examination of the milk from 50 herds supplying Ithaca, New York, showed the presence of *Brucella abortus* in the milk of nine".

Zwick (1930) (39) estimated the annual loss due to Bang's disease in Germany to be at least 250 million reichsmarks.

Holth (1930) (50) states, "During the period 1912-1929 blood and other material have been tested at this Institute (State Veterinary Institute, Oslo, Sweden) from a total of 16,743 cows which had aborted. Of these, 4,511 gave distinctly positive reactions and 297 suspicious reactions for infectious abortion, in all 28.72 per cent. The cows in question were distributed amongst a total of 12,905 herds, of which 3,659 (28.35 per cent) were found to be infected or were suspected. The number of cases of sporadic abortion which were not produced by specific abortion bacilli thus becomes relatively large, in that infectious abortion is not spread regularly over the whole country, the majority of cases occurring in definite districts". This statement brings out the well known fact that not all cattle abortion is true brucellosis.

Gibbs, C. S., Chen Ken and Sheo Piao (51) first found a case of infectious abortion in China in an imported cow in 1923. The next case was in a native heifer bred to a foreign bull. They tested 128 head of foreign cattle by the agglutination test. Of these, 88 were negative, 38 gave positive reactions, and two were doubtful. Of 25 native cattle tested only two were positive. They tested the blood of 63 water buffaloes, 57 were negative, three gave weakly positive, and three strongly positive results. They



do not know whether the water buffalo is susceptible to the infection. In this connection, it is interesting to note the results of agglutination tests on the blood of a small number of elk, (p. 32, Report of Chief of B. A. I., 1930). Of six samples, one female reacted 1 to 200 and one male reacted 1 to 100 (Cotton) (52).

Henricsson (53) furnishes a graph and additional data from which Graph I is reconstructed. The additional data on the number of cases of cattle abortion in Sweden are given below. Bacteriological and serological tests began only in 1912.

Year	Number of herds	Number of cases
1927		(Highest) 8,208
1928	1,305	6,649
1929	1,381	7,628
1930	1,764	6,899

Swine Brucellosis

Johnson and Huddleson (1931) (54) give the following table on a comparison of results on hogs reacting to the agglutination test conducted in three different states,—one Eastern, one Western and one of the Great Lakes States.

Reported by:	State	Hogs Tested	Number of Reactions in Dilution of:			
			1:20-25	Per cent	1:40-60	Per cent
Hardy and Associates.....	Iowa	343	98	28	74	21
Boak and Carpenter.....	New York	4,014	—	—	64	1.34
Johnson and Huddleson....	Michigan	1,672	336	19.9	134	7.99

The same authors state that, "The field survey indicates that the disease is very prevalent in hogs in the state of Michigan".

Thomsen (55) reported an outbreak of swine brucellosis which spread to 150 herds in central Jutland and was carried to Seeland by infected animals sold there. All the cultures isolated grew aerobically in the first generation. Transmission from hogs to cows and vice versa was not demonstrated. The disease in Denmark has been limited to this outbreak.

Undulant Fever of Man

Hardy, et al. (1930) (9) presented a mass of statistical evidence on undulant fever in the United States and especially in Iowa. The following table is taken from their report (p. 30):

Distribution by age groups of the Iowa cases on whom the necessary data were available:

Age	Total	Males	Females	Cases having had contact with livestock or carcasses	Cases having had no contact with livestock or carcasses
0-4.....	4	2	2	0	4
5-9.....	8	5	3	0	8
10-14.....	15	10	5	5	10
15-19.....	27	22	5	12	14
20-24.....	43	41	2	32	8
25-29.....	42	34	8	28	12
30-34.....	41	31	10	28	12
35-39.....	58	50	8	39	13
40-44.....	43	34	9	26	15
45-49.....	25	20	5	16	7
50-54.....	24	16	8	14	8
55-59.....	5	2	3	1	4
60-64.....	9	5	4	3	6
65-69.....	5	3	2	2	2
70-74.....	3	2	1	1	2
75-79.....	2	0	2	2	0
Total.....	354	277	77	209	125

This table gives interesting data on sex occurrence of the disease. The following paragraph deals with the influences of occupation: "The distribution according to occupation was as follows: Farmers (including sons and farm laborers), 162 (44.7 per cent); women on farms, 24 (6.6 per cent); stock buyers, 5 (1.4 per cent); packing house employees, 37 (10.2 per cent); butchers, 2 (0.55 per cent); housewives (other than farmers'

wives), 37 (10.2 per cent); students, 18 (4.9 per cent); children, 19 (5.3 per cent); professional and business persons and laborers, 58 (16 per cent)".

Their data on seasonal distribution were confined to the records of only two years (1928 and 1929) and, while not conclusive, indicated a greater incidence of the disease in the summer months, but with cases every month of the year.

Hardy et al. (1932) (56) made a further study of *Brucella* infection in Iowa for the period, March 1, 1930 to March 1, 1931. They make this significant statement, "The evidence, however, again justifies the assertion that the graver forms of the disease are of infrequent occurrence and that as a general health hazard undulant fever is of relatively minor importance". The occupational status of 113 cases was: Farmers, 51 (46 per cent); farmers' wives, 9 (8 per cent); packing-house employees, 6 (5.5 per cent); butcher, 1 (1 per cent); stock buyers, 1 (1 per cent); laborers, professional or business man, 28 (25 per cent); housewives, 10 (9 per cent); and school children 5 (4.5 per cent). There were 89 (79.5 per cent) males and 23 (20.5 per cent) females and 40 cases (23 males and 17 females) reported as having had no contact with livestock. Where the patients have had direct contact with the usual livestock on an Iowa farm, serological evidence points to cattle as a probable source of infection in only about one-half of the cases; but where the patients have had no direct contact with livestock, a thorough examination of the dairy herds concerned usually reveals positive reactors".

A similar comparison was made with cases having contact with herds of hogs. Their findings indicate that cattle and hogs are of about equal importance as the source of *Brucella* infections among Iowa farmers. It seems that the transmission of the disease from hogs to cattle or from cattle to hogs is rare if it occurs at all.

Kristensen (1931) (57) reported on the basis of records in the Danish National Serotherapeutic Institute. The table (p. 77) comprises all the cases observed in Denmark from April 1, 1927 to December 31, 1930:

	Males		Females		Total	
	Number	Rate per 1,000	Number	Rate per 1,000	Number	Rate per 1,000
Capital—Copenhagen.....	117	0.35	60	0.15	177	0.24
Other Cities:.....	185	0.46	73	0.16	258	0.30
Rural.....	989	1.06	215	0.24	1,204	0.65
Total.....	1,291	0.78	348	0.20	1,639	0.48

From an occupational standpoint he found the following distribution of cases: Animal husbandmen 14 per 1,000; veterinary, 5 per 1,000; butchers 3.3 per 1,000; farmers (other than animal husbandmen) 1.8 per 1,000; persons whose business did not cause them to make contact especially with animals, 0.66 per 1,000.

There was no especially peculiar seasonal distribution during the years 1928-1930.

The Table (p. 86) is of interest in that it shows age, sex, and occupational relationships.

Age	Contact (animal)		Milk		Questionable		No information received		Total	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
0-4.....	—	2	1	—	—	1	—	—	1	3
5-9.....	5	—	8	8	2	3	1	—	16	11
10-14.....	24	8	15	14	5	3	3	—	47	25
15-19.....	109	20	31	10	20	6	12	2	172	38
20-24.....	108	10	28	15	34	4	6	2	176	31
25-29.....	135	13	44	15	34	10	4	1	217	39
30-34.....	113	15	47	20	23	8	7	2	190	45
35-39.....	69	10	29	17	15	3	3	1	116	31
40-44.....	59	7	30	15	19	6	5	3	113	31
45-49.....	43	9	30	3	8	12	4	2	85	26
50-54.....	24	8	15	10	9	1	4	3	52	22
55-59.....	14	4	15	8	8	1	3	1	40	14
60-64.....	13	5	3	5	2	5	2	1	20	16
65-69.....	4	1	1	4	2	—	—	—	7	5
70.....	1	—	1	2	—	2	—	—	2	4
Unknown.....	27	2	9	2	4	1	4	3	44	8
Total.....	748	114	307	148	185	66	58	21	1,298	349

Kristensen (57)

Zeller (58) (p. 295) reports for Germany on the following 626 cases:

**Distribution of Bang's disease of man in Germany by age and sex
(Oct. 1, 1929 to Sept. 9, 1930)**

Age—years	Male	Female	Sex not given	Sex and age not given
To 3.....	—	1	2	—
4-9.....	13	2	—	—
10-14.....	11	4	—	—
15-19.....	34	13	1	—
20-29.....	113	39	—	—
30-39.....	94	39	—	—
40-49.....	65	34	—	—
50-59.....	35	20	1	—
60-69.....	10	5	—	—
70-75.....	1	2	—	—
Unknown.....	54	28	—	—
Total.....	430	187	4	—

He also gives the following information on the sources of infection of these 626 cases (p. 296):

Contact with abortion-cattle	Use of raw milk and milk products	Contact with abortion-cattle and raw milk, etc.	Laboratory infection	Other causes	Unknown causes and not specified
124	211	53	9	13	216

Also the distribution of human Bang's disease by occupation :

1. Agriculture (husbandman, breeders, herdsmen, servants, hired men, cattle dealers, etc.)	172
2. Dairying (milkers, peddlers, dealers, etc.)	49
3. Meat trade (butchers, cutters, skimmers, etc.)	15
4. Artisans and tradesmen (inn keepers, locksmiths, carpenters, masons, harness-makers, merchants, gardeners, etc.)	58
5. Physicians (includes one with undulant fever contracted out of Germany)...	4
6. Veterinarians	14
7. Laboratory personnel (students, technical assistants, laboratory helpers and scrubwomen)	8
8. Officials, teachers	37
9. Laborers	20
10. Housewives	32
11. Other callings (tailors, waiters, hairdressers, bookkeepers, photographers, employers, etc.)	56
12. Occupation not given	131
Total	626

The monthly Epidemiological Report of the Health Section of the Secretariat of the League of Nations, October 15, 1930, gives some statistics covering the world wide situation (p. 410).^{*} (The material presented on pages 22-25 is based on these reports.)

The report also gives a tabulation (p. 416) of the age and sex distribution of *Br. abortus* Infection in Sweden (after Kling)

Age.....		0-11	11-20	21-30	31-40	41-50	51-60	61-70	71 +	Total
Individuals with an agglutinating serum (concealed infections).	Males.....	0	1	4	14	10	6	3	0	38
	Females....	4	8	26	35	16	10	7	1	107
	Both sexes..	4	9	30	49	26	16	10	1	145
Undulant fever cases.	Males.....	0	11	9	14	8	4	0	0	46
	Females....	0	1	6	2	4	4	0	1	18
	Both sexes..	0	12	15	16	12	8	0	1	64

^{*}There is an excellent summary of recent literature (168 titles) dealing with the epidemiology of undulant fever.

Number of cases of Undulant Fever in countries where notification is compulsory

Country	1925	1926	1927	1928	1929	1930	Up to:
Europe:							
Sweden.....	—	—	—	56	118	65	9-30
Denmark.....	—	—	—	372	503	372	9-30
France.....	110	134	190	124	155	164	9-30
Italy.....	1,439	1,085	1,071	959	956	—	—
Yugoslavia.....	0	0	0	3	1	0	10-31
Greece.....	1	0	0	3	13	35	10-31
Malta.....	663	596	702	972	1,288	1,084	8-31
Africa:							
Algeria.....	10	25	23	19	20	17	9-8
Tunis.....	46	17	50	21	28	26	9-8
Morocco.....	—	—	1	0	6	10	10-31
Southern Rhodesia.....	13	10	8	0	2	2	10-18
America:							
United States.....	24	45	217	647	1,505	—	—
Total.....	2,306	1,912	2,262	3,176	4,555	1,775	—

The first General Review of Undulant Fever was published in the Monthly Report of June 15, 1927, p. 329. According to this report, "Undulant fever occurs in most Mediterranean countries, without being very common in any except Malta, where its incidence has varied in recent years between 2.7 and 5 per 1,000 inhabitants.

"The number of cases in the Maltese islands decreased from 1,102 in 1902 to 602 in 1926. During the first quarter of the current year (1927), there were more cases, however, than during the corresponding period of the two previous years. Its case mortality was 4.5 in 1926, and it has usually been between 4 and 5 per cent.

"June and July are usually the months of maximum incidence in Malta. In Italy, the seasonal maximum occurs in May and June, and in France in April.

"It appears to have been eradicated from Gibraltar; at any rate, no case has been reported during the last 18 months."

The second General Review was published in the Monthly Report of May 15, 1928. Attention was called to undulant fever in Iowa, where it was reported as prevalent as typhoid fever, and in New York State. It was reported to be due in these cases to cow's milk. In Denmark, reporting began in the latter part of 1927, 62 cases occurring in the first quarter of 1928 (at the same time only 27 cases of typhoid and 19 cases of paratyphoid being reported). An excess of males was reported contrary to the reports from Malta. In Malta, in 1924-1926, there were 53 deaths in males and 65 in females. In both Denmark and Malta, the disease was rare in children. Twenty-four cases were reported at Pignan, Department of Hérault (southern France) monthly from December, 1923-May, 1924, all in men.

The following Tables contain the data on undulant fever from each country from which official reports are received. The data are found in the Monthly Epidemiological Report of the Health Section of the Secretariat of the League of Nations (Geneva), 1927, pp. 343, 425, 505, 585; 1928, pp. 122, 206, 363, 479; 1929, pp. 142, 226, 374; 1930, pp. 32, 228; 1931, pp. 22, 154, 411; 1932, pp. 98, 248. (Since March-April, 1932, the Reports have appeared every other month.)

Quarterly reports on the occurrence of Undulant Fever in several countries. 1926-1932

	1926			1927			1928			1929			1930			1931			1932																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																
Country	2nd Quarter	3rd Quarter	4th Quarter	Total 3 Quarters	1st Quarter	2nd Quarter	3rd Quarter	4th Quarter	Total	1st Quarter	2nd Quarter	3rd Quarter	4th Quarter	Total	1st Quarter	2nd Quarter	3rd Quarter	4th Quarter	Total	1st Quarter	2nd Quarter	3rd Quarter	4th Quarter	Total																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																											
Algeria.....	15	4	8	27	7	14	0	3	24	7	10	6	1	24	1	9	3	7	20	4	9	5	4	19	5	11	0	5	21	3	2																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																				

MICHIGAN STATE EXPERIMENT STATION

Monthly reports on the occurrence of Undulant Fever in several countries—1926-1932

Country	1926												1927												1928				
	April	May	June	July	August	September	October	November	December	Part of Total	January	February	March	April	May	June	July	August	September	October	November	December	Total	January	February	March	April	May	
France.....	46	20	4	4	3	4	0	3	17	101	5	5	18	39	65	19	9	7	13	3	6	1	190	9	14	14	14	24	
Malta.... { C	48	41	83	91	70	78	58	33	34	536	20	38	42	45	61	69	90	80	62	88	66	42	703	38	39	46	62	84	
Malta.... { D	2	2	3	3	1	7	0	2	4	24	2	3	0	2	0	5	3	3	4	1	1	4	28	1	0	2	1	3	
Denmark.....																							9	16	37	47	35		

Country	1928—Continued												1929					1930											
	June	July	August	September	October	November	December	Total	January	February	March	April	May	June	July	August	September	October	November	December	Total	January	February	March	April	May	June	July	
France.....	20	10	12	0	1	3	3	124	3	4	32	11	29	18	19	27	7	2	1	2	155	9	14	18	20	46	32	12	
Malta.... { C	117	184	144	85	89	46	38	972	36	24	47	75	131	199	191	190	154	103	72	66	1288	66	61	97	107	138	195	247	
Malta.... { D	5	8	7	4	3	3	3	42	1	3	2	3	4	7	13	9	7	3	5	4	61	2	5	4	6	7	8	11	
Denmark.....	46	37	36	29	36	26	36	390	32	26	41	42	46	68	50	54	39	51	40	37	526	36	41	39	35	58	35	27	
Sweden.....		4	9	13	16	8	6	56	3	10	11	13	12	11	8	13	8	10	9	10	118	9	7	10	7	11	6	6	
Canada.....																							7	7	6	11	10		

C—Cases D—Deaths

Monthly reports on the occurrence of Undulant Fever in several countries—1926-1932—Continued

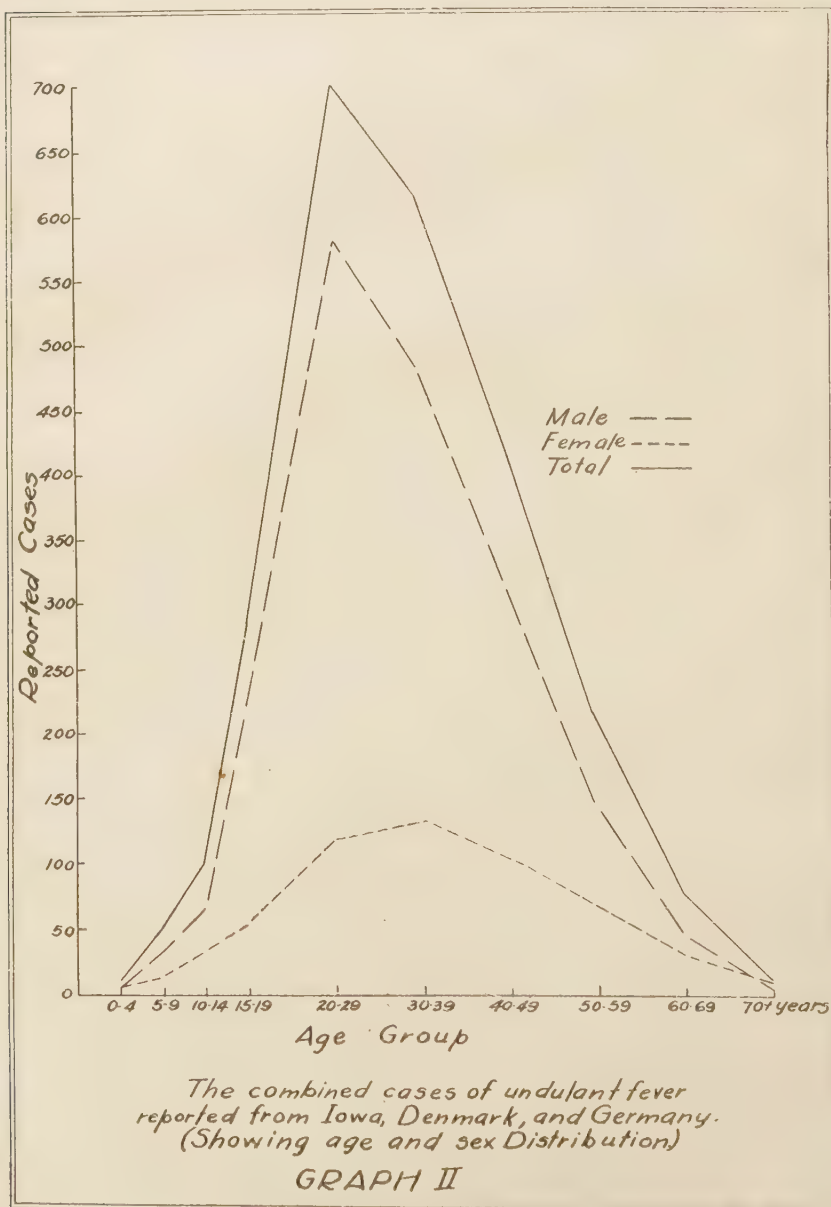
Country	1930—Continued					1931										1932												
	August	September	October	November	December	Total	January	February	March	April	May	June	July	August	September	October	November	December	Total	January	February	March	April	May	June	July	August	September
France.....	7	6	3	2	6	175	21	8	15	17	40	34	22	13	1	6	5	4	186	7	19	40	45	31	54	26	23	9
{ Malta . . . { D	173	139	106	76	68	1473	73	54	77	67	152	149	186	178	151	123	89	50	1349	61	68	89	92	132	137	198	211	179
	15	8	8	7	4	85	4	5	2	4	3	10	16	12	5	4	2	5	72	3	1							
Denmark.....	48	53	43	52	54	521	49	42	58	52	46	67	46	51	54	49	37	36	587	40	47	46	54	42	45	43	36	44
Sweden.....	5	4	10	8	12	95	6	12	9	11	11	14	17	12	16	6	4	9	127	8	7	13	18	9	7	9	10	8
Canada.....	10	0	13	6	4	74	15	14	10	9		11	24	31	9	8	10	6	147	3	7	4	5	9	5			
United States..					109	109	96	83	83	109	119	136	145	128	112	120	124	109	1364	70	85	77	90	104	142	168		

C—Cases D—Deaths

Zdrodowski et al. (1930) (59) report that reactors in native cattle in Azerbaidjan are rare but that the *Brucella* infection exists in imported cattle. They give statistics on the occurrence of undulant fever as follows:

Total number of persons examined, 1,292; found infected, 60, 4.6 per cent.

Total number of goats and sheep examined, 1,973; found infected, 35, 3.2 per cent.



Only 0.7 per cent of 803 cattle reacted positively.

In a dairy at Bakou they found:

Number of workers examined, 142; found infected, 4, 2.8 per cent.

Number of cows examined, 303; found infected, 6, 2.0 per cent.

Some data of limited statistical value are available as a result of testing blood samples collected from selected or unselected cases or submitted to public health laboratories for Wassermann, Kahn or Widal tests. Thus, Mallick and Ahuja (1931) (60) in India tested 487 sera from healthy and febrile cases and found agglutinins for *Brucella* in both groups.

Bigger (1931) (61) in Ireland tested 500 sera of which 100 showed agglutinins in a dilution of 1-20, 22 at 1-50, 10 at 1-125, and none at higher dilutions. He concluded that clinical undulant fever is rare in Ireland.

Davies and Anderson (1929) (62) reported the first case of *Br. abortus* infection in man in Wales.

Lentze (1930) (63) in Germany tested the blood of 74 healthy individuals from 20 manors in which infectious abortion of cattle was known to be prevalent. Of 57 who came in contact with cattle, over 20 per cent reacted. Of 17 who had been drinking in large quantities the raw herd milk known to contain the organisms, but who had not come in contact with infected cattle, none gave a positive reaction. Only males reacted and only one reacting individual had symptoms attributable to *abortus* infection.

A great deal of blood testing has been done in the United States. Carpenter et al. (1930) (64) tested 4,050 Wassermann blood samples at Syracuse, N. Y., and found 7.6 per cent to contain *abortus* agglutinins. Examination of 955 similar samples collected in New York City showed 2.4 per cent to agglutinate *Br. abortus*. *Br. abortus* agglutinins could not be demonstrated in the serum from adults who had been drinking pasteurized milk containing such antibodies.

Graph II is based on the combined data from the tables which show the age and sex incidence of undulant fever in Iowa (page 18), Denmark (page 20), and Germany (page 20). The curves are fairly good standard distribution curves.

These data are consolidated in the accompanying table:

Age Group	Danish		German		Iowa		Total		
	Male	Female	Male	Female	Male	Female	Male	Female	Total
0-4.....	1	3	0	1	2	2	3	6	9
5-9.....	16	11	13	2	5	3	34	16	50
10-14.....	47	25	11	4	10	5	68	34	102
15-19.....	172	38	34	13	22	5	228	56	284
20-29.....	393	70	113	39	75	10	581	119	700
30-39.....	306	76	94	39	81	18	481	133	614
40-49.....	198	57	65	34	54	14	317	105	422
50-59.....	92	36	35	20	18	11	145	67	212
60-69.....	27	21	10	5	8	6	45	32	77
70 Up.....	2	4	1	2	2	3	5	9	14
Totals....	1254	341	376	159	277	77	1907	577	2484

Cases of Undulant Fever in the United States, 1929 to

State	January				February				March				April				May				June				July								
	1929	1930	1931	1932	1929	1930	1931	1932	1933	1929	1930	1931	1932	1933	1929	1930	1931	1932	1933	1929	1930	1931	1932	1933	1929	1930	1931	1932	1933				
Alabama . . .		1	1		1	1		3	1	2		1				2		4	3	4	2	1	1	1	5	3		1					
Arizona	3	1		1	1	2			1	1			1	1	1	1		1	3		1		1	4		3	3	1	5	1	1	1	
Arkansas					1	1				1				1				1						1					5				
California . . .	2	9	8	6	4	1	7	6	6	8	5	8	9	5	8	6	8	7	10	13	6	6	7	6	11	6	13	9	14	7	5	12	12
Colorado . . .				1			1	3				1		1						1				1					1		24		
Connecticut	4		2	4	1		3	3	4			2	3	4	1	1	3	1	2	2	1	2	1	1		2	1	7	2	2	1	2	
Delaware	1			1	1	2				1				1																2	1		
Florida		2	1			2								1				1					1	1					1				
Georgia				1	1	1		3	1			3	1		1		2	5		3			1	2		6		5	7		5	1	
Idaho																		1			6		1			12		1			2		
Illinois	1	2	5	7	3		6	5	4	10	2	6	15	5	8	2	6	22	6	4	2	6	25	7	10	3	8	5	6	6	5	10	16
Indiana		1	2	1	6		1	2		4		2	1			3		2				6	4	4			4	2	3	1		5	
Iowa	2	13	10	8	5	6	14	3	4	6	13	10	2	4	8	19	12		8	23	12	13	3	5	18	16	24	4	10	24	15	15	4
Kansas	8	10	8	1	1	1	2	1	1	1	2	3	1	1	3	6	8	7	1	2	6	9	2	4	12	4	13	6	10	12	11	17	
Kentucky																								2	1					8			
Louisiana			3	1	2		7	1	1		2	2	1		4	4	2	5		1	1		5	3	3	4		3	4	1	6	2	4
Maine				2	1	1	1	1	1		2	1			3	1	1	1			1			6		2		1	2			1	
Massachusetts	4	2			1					2	3	2			1		1	1	2		1		1	1	1		1	3	2	1	1	1	
Maryland	2		7	1	1	2		4	2	2	3	3	1	4		2	1	4	3	4	1	2	5	3	2	3	7	2	8	3	4	7	
Michigan	1	2	1	5		2	2	5	6	1	1	2	3	1		2	2	5	4		1	1	1	8		1	1	2	17		3	1	
Minnesota . . .	1	3	4	3	7	1	2	6	2	1	5	2	3	3	3	7	3	5	2	3	2	8	6	8	5	4	5	5	7	5	10	8	5
Mississippi . . .				2				1				1	1					1	1		1		2			1		1			2		
Missouri		5	8	1	8		12	3	3	2		6	6	5	20		10	8	9	5	1	8	10	12	1		18	24	15	37		17	20
Montana	1			2		1					1	2	1							2	1				3		1		3	3		1	
Nebraska	1					1				1	1					1									2		2		1				
Nevada												1																		1			
N. Hampshire						1				1												1											
New Jersey . . .	2		4	4	3		2	3	3	7	3		4		1	1	1	3	2	1			2	3	2	2		2	5	5	1		3
New Mexico . . .		1																1					1			1	1	1	2			1	
New York	3	9	18	7	21	4	7	18	20	20	5	7	13	19	22	4	13	16	13	25	10	13	12	13	25	11	6	28	18	29	14	11	8
No. Carolina . .				1		1			3					2						1				1	1			1	1				
North Dakota . .	1			1		2	1		1			1		1		2				1	1	2			1		1				2		
Ohio	2	10	7	7	5	11	4	13	2	2	2	2	5	6	7	3	8	14	3	8	11	37	10	4	9	6	10	13	10	4	4	10	7
Oklahoma			1		1			1					1						2	1			1									1	
Oregon	1	3		3		1		2	1		3					2	6			2	1	2	1		1	2	1	1		1	5		1
Pennsylvania	1	7		2	1	5	2	3	3		5	3	1	1			2	1	6	2		4	3	8	8	1	1	1	7	3	2	4	1
Rhode Island . .	1			1		1			1																								
So. Carolina . .				1	1						1		1									1	1			1				2		1	

clusive, as reported to the U. S. Public Health Service.

August				September					October					November					December					Year 1929	Year 1930	Year 1931	Year 1932	Year 1933
1929	1931	1932	1933	1929	1930	1931	1932	1933	1929	1930	1931	1932	1933	1929	1930	1931	1932	1933	1929	1930	1931	1932	1933	1929	1930	1931	1932	1933
1	3	4	1	3	2	1	2		3	2			1	3	2			1	3	2			1	5	4		4	17
3		1	2	1		1	5	6		1	3	1	1	3		2			2	2	1		1	2	1		13	16
			1				1							1									1				2	2
9	4	9	13	5	13	10	9	12	14	10	9	7	11	9	13	8	7	13	4	7	8	10	12	72	115	97	103	128
	5	3	1				1		1			1		1				1		2				5	2	31	9	4
1	1	3	4	3				6	1	1		1	4	2	2	3	8	5		9	2	2	1	12	22	19	33	37
2				1			1	1	2					1			1	3					1	5	8	2	2	6
			2	1								1		4									1	9	4	1	2	6
5	2	2	5	4	3	3	4	18	6	2		2	3	2	3			1					3	3	13	29	6	28
	2	1	6			1		2	1	2			3					2								1	2	16
10	8	7	7	3	2	5	5	8	5	4	6	8	8	8	5	12	8	11	4	4	3	1	12	39	69	127	77	95
5	1	3	1	3	3	1			2		8	6	1	4		4	3	1	1		1	4		13	28	27	27	15
15	4	15	15	26	7	2	13	10	13	8	4	3	4	4	11	7	4	10	11	10	5	4	5	158	152	48	86	151
17	5	6	4	16	9	3	7	8	4	10	2	5	2	4	6	7	1	2	5	10	5	1	10	85	114	47	41	59
				3				1	4										1					13	8	0	0	0
2	3	3	1		2	11	4	6		2	11	2	2		4	2	5	1	1	3	2		3	17	19	58	32	27
		1	1	1		2	1					6	5				1	2	1	2		1	4	8	9	5	15	23
1	2	2	2	1		1			1	3		3			3	1	2	2		2	1	1		8	12	16	15	11
4	9	6	2	2	5	4	11				3	3	3	1	6	4	3	4	1	1	3	3	6	17	33	43	50	37
3	1	10	7		1	1	3	12			3	3	5		1		2	4	2	1	3	3	5	4	17	19	44	83
8	6	9	10	5	8	5	2	5	3	8	4	3	7	1	3	9	3	12	3	9	2	5	6	45	67	60	58	65
2		2	3	1	1		2					1	3		1	2		1		1	1		2	3	9	3	12	14
17	20		1	26	10	13	30	2	12	6	8	18		5	10	8	11	2	5	4	6	8	1	50	123	134	147	79
			2				1					1	3			2	1					2		3	3	4	11	17
				3	1			1	1		1				2			1	3		1		1	8	8	4	1	5
								2						1										3	0	0	1	1
				2																				3	2	0	0	0
	3	6	2		1	2	2		2	5	7	2			5	10	3	1		3	2		4	11	17	45	31	27
				2		1	1	1					1			1	1							2	2	5	3	7
11	11	19	24	8	29	10	23	31	19	29	17	22	12	13	18	22	3	19	6	15	23	30	45	104	168	196	209	292
			1				1	1				1	3		1		1					1	1	1	2	0	5	15
2					1			2	1				1			1	1			1				5	12	6	1	4
10	12	12	9	10	13	8	6	14	8	7	12	7	4	9	12	3	6	6	3	5	11	3	1	73	128	115	87	77
	1				6		4		2	2		2	1		1		1	1				1	2	3	2	13	5	12
	2			3	2		5	6	2	2	3	1	2		3	2			3	2	1		2	19	25	11	11	16
4	3		7	11	1	6	2	5	1	3	4	3	4	2	4	2		2	1		6	10	8	25	34	39	45	52
												4						1	2				2	2	2	0	0	11
1			1		1					2		1		1									3	0	7	3	3	10

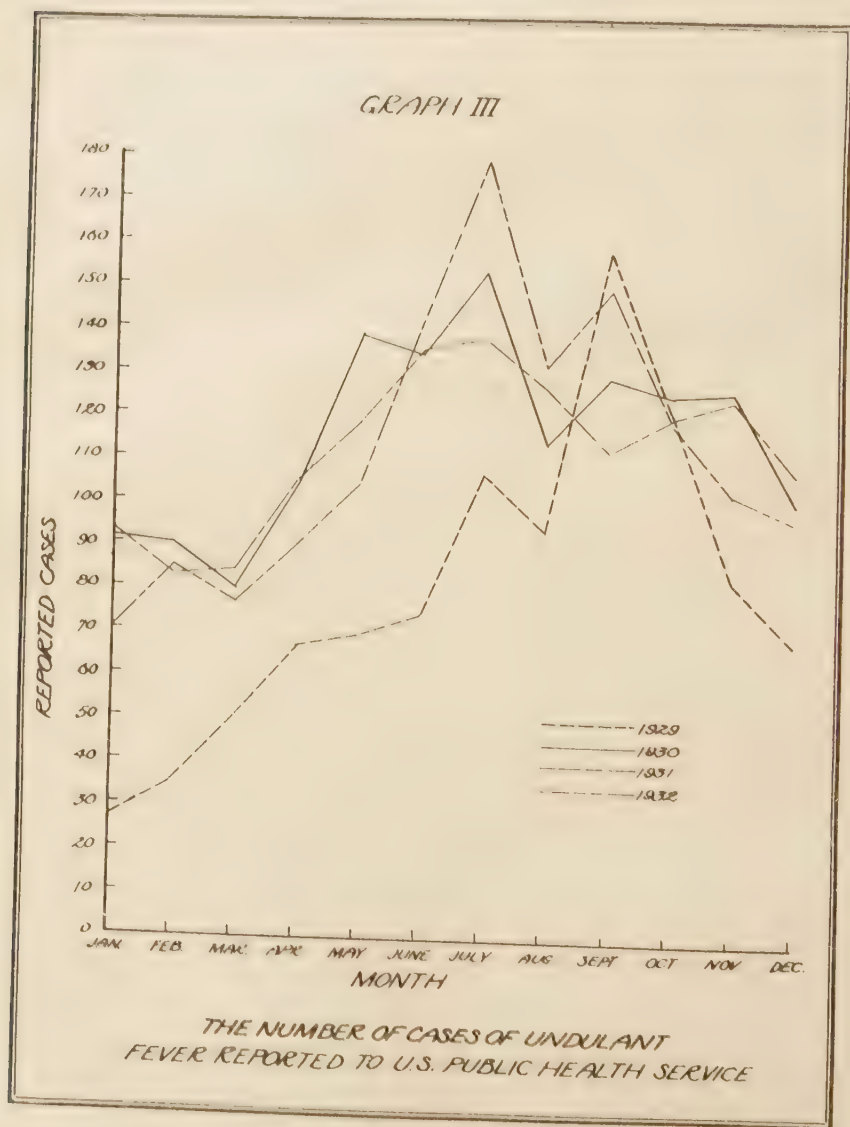
Cases of Undulant Fever in the United States 1929 to 1933 inc

State	January				February				March				April				May				June				Ju								
	1929	1930	1931	1932	1933	1929	1930	1931	1932	1933	1929	1930	1931	1932	1933	1929	1930	1931	1932	1933	1929	1930	1931	1932	1933	1929	1930	1931	1932	1933			
South Dakota.										1				1											1	1							
Tennessee. . .		1		3			1		1		1	1	1	1							1				1		1		3				
Texas.												1							1	1													
Utah.																																	
Virginia. . . .				2	1	1			6	4	1			2	1				4	1	4	1		2	1	2	1	1		8			
Vermont.		2	1		1		1	2	1	1	4	1		4		1	1			1	2	1	2				1						
Washington. . .			1	1	2		3	1	2	4	2	2	1	2	1	1	4	1	3	1	2	1	2	5		4	1	1	2		6		
Wisconsin. . . .	2	1		1	3	2	3	1		2	7	4	3		1	2	3		6	6	5		6	3	5	4		3	3	7	7	3	
West Virginia.											1	1		1																			
Wyoming.							1			1		1																					
Total.	27	91	93	70	98	35	91	83	85	100	49	81	87	73	111	67	104	104	90	121	70	138	119	103	154	74	134	136	146	210	107	153	138

reported to the U. S. Public Health Service.—Continued.

August				September					October					November					December					Year 1929	Year 1930	Year 1931	Year 1932	Year 1933
1930	1931	1932	1933	1929	1930	1931	1932	1933	1929	1930	1931	1932	1933	1929	1930	1931	1932	1933	1929	1930	1931	1932	1933					
3	1					2		1		1	3							1					1	0	4	6	4	6
3	2				1		1	4						2	1		2	2			1		1	5	11	7	10	8
													1		2			11						3	3	0	0	18
																								0	0	0	0	0
3	2	4	4	2	1	3	2	6		1	2	3	3	1	1	3	1		1	3	1	1	4	24	16	33	29	
2	2		1		2	2		1	2	2			1	2	1				2	3	1		2	19	15	6	13	
2	7	1	2	10	5	3	3	1	8	1	5	1	2	7	1	2		3		6	2		23	33	33	20	26	
2	5	3	7	5	2	4	2	3	5	8	1	4	10		7	1	9	1	2	3		4	42	28	39	25	59	
													1										0	1	1	0	2	
													1					1					2	2	0	0	1	
148	127	132	149	158	128	112	149	176	121	125	120	119	117	83	126	124	83	133	68	101	108	97	155	952	1420	1351	1326	1659

Graph III is based on a graph given by Hasseltine (65) showing the 1929 and 1930 incidence of undulant fever in the United States. The 1931 and 1932, data are taken from the U. S. Public Health Service, Public Health Reports, volumes 46, 47, and 48. It is known that these reports are not complete. For example, Simpson (66) reported finding 1,305 cases for the year 1929.



What is the Relative Importance of Undulant Fever as a Public Health Problem?

Any disease which affects a considerable percentage of the people is important but it is not possible mathematically to measure the importance of a disease solely on the basis of its occurrence or its relative importance on the basis of the frequency of its occurrence in comparison to that of all other diseases. The case fatality is of especial importance. For example there were 170 times as many cases of chicken pox as of undulant fever in the United States in 1931; but the latter disease is 30 to 66 times as fatal as is the former. Furthermore, there are other factors that must be considered in an effort to determine the relative importance of diseases: Are the statistics complete? Are they accurate? Are the diseases comparable with respect to their severity, duration and complications? Do they have the same economic implications? It is obvious that there is no reliable formula whereby either the absolute or the relative importance of any disease as a public health problem can be determined accurately without ready access to more or less complete and reliable data with respect to all or many of its manifestations, occurrence, fatality, severity, duration, complications, and economic implications.

No attempt is made or need be made to contrast undulant fever with such diseases as human tuberculosis and the venereal diseases. Hence no data are included with regard to these diseases. They are public health problems of the first magnitude.

In 1931, typhoid fever appeared to occur over 18 times as frequently as undulant fever. It is also four to six times as fatal and not less serious in its general manifestations. Certainly, therefore, brucellosis is measurably less of a public health problem than is typhoid fever, although it may be a greater problem in sections where adequate measures have been taken to combat the latter disease and inadequate measures are enforced against the former disease.

There is no recognized boundary between major and minor public health problems. Undulant fever is certainly near any boundary line that might be selected in so far as frequency of occurrence is concerned. In respect of case fatality, it would also take rank near a median position. The severity of the disease is variable, as is the case with most diseases, but it is a fair estimate to state that brucellosis of man is characterized by symptoms suggestive of such severe diseases as malaria, typhoid fever, tuberculosis, pyogenic infections, or influenza. There is a pyrexia usually accompanied by obstinate constipation, progressive anaemia, and debility. It is often complicated with, and followed by neuralgic symptoms referred to the peripheral or central nervous system; arthritic effusions; painful inflammatory conditions of certain fibrous structures, of a localized nature; or swelling of the testicles.

"Though the mortality rate is low, the invaliding rate is high, and the duration prolonged, so that the average stay in hospital is seventy to ninety days." (Hughes, p. 3) (1).

The reaction of the patient to brucellosis and its economic importance may be inferred from the quotation from Hughes whose description of the disease is applicable to the cases that occur in this country. The economic importance of undulant fever is out of proportion to the total number of cases or even to its average severity since the largest number of cases occur

in adult males who are most frequently the wage earners and consequently the support of the family. This is quite in contrast to many of the diseases of childhood the case frequency of which is a hundred times or more that of brucellosis.

The importance of a disease may be considered from the standpoint of its mode of dissemination which may be the determining factor in the program of control. Brucellosis is not considered and it certainly is not commonly contagious from man to man. Thus, it lacks entirely the social significance of the human infections that have the greatest case frequency and that are spread by inter-human contacts. As a public health problem, brucellosis is a minor major problem or one of the major minor infectious disease problems.

Compared to other infectious diseases of animal origin brucellosis looms larger. It is certainly comparable in importance to bovine tuberculosis as a disease of man both in respect of the frequency of occurrence and importance of the disease to the individual as well as of some of the methods of control. However, the comparative importance of the two diseases of bovine origin is influenced by the measures that have been taken to control the one or the other disease in cattle or otherwise to prevent their dissemination. In Michigan, due to a vigorous and successful campaign of eradication, it is hardly conceivable that there have developed more than the rarest of new cases of bovine tuberculosis in man during the past few years. On the other hand, there have certainly developed, annually during recent years in Michigan, several dozen cases of undulant fever, many of which are of bovine origin. Undulant fever is more important from the standpoint of frequency of occurrence than any other disease of domesticated animal origin except tuberculosis, at least in the United States.

An editorial in the American Journal of Public Health* calls attention to the serious situation in regard to bovine tuberculosis in cattle and consequently in children in Great Britain. It states that in that country 40 per cent of the cattle are infected, an average of 6.7 per cent of the market milk contains bovine tubercle bacilli and that 2,000 deaths and at least 4,000 new cases of bovine infection, mostly in children, occur annually. Considering the situation in the United States the editorial interprets certain data to mean "that 3,500-4,000 children annually die in this country from bovine tuberculosis, and that at least 8,000 cases occur"; yet, the editorial continues, "the National Tuberculosis Association, which enjoys a rich income from Christmas Seal sales, amounting one year to approximately 5½ million dollars, and altogether something more than 65 million dollars, has done nothing except pass resolutions concerning tuberculin testing, pasteurization, accredited herds, etc".

"The public owes a debt of gratitude to our Bureau of Animal Industry and to state and city officials in their efforts to suppress bovine tuberculosis, but practically nothing to the National Tuberculosis Association, —. The suppression of bovine tuberculosis by the Bureau of Animal Industry is largely a commercial affair, though many veterinarians are deeply interested in the danger of bovine tuberculosis to human beings—more so apparently than the members of the National Tuberculosis Association."

In 1931, there were reported to the U. S. Public Health Service 1,346 cases of undulant fever, 4,147 cases of septic sore throat, and 543 cases of paratyphoid fever. The seasonal and geographical distribution of these

*Vol. XXII, No. 8, August, 1932.

three diseases shows no unusual peculiarities. Paratyphoid fevers are frequently of animal origin or are spread by animal products, but they are in no sense comparable to brucellosis in importance as a human disease problem.

In his *Preventive Medicine and Hygiene*, Rosenau writes of septic sore throat, "Apparently it is not readily communicable from person to person". How then it is communicated? Probably by milk, in many if not all cases, by milk of infected cattle. If only one-third of the cases of septic sore throat are of bovine origin, then this disease is more important than brucellosis at least as regards frequency of occurrence. It is also on the whole probably a more serious disease in respect of fatality and at times ability to incapacitate the patient. It is easy to conclude that, of diseases of bovine origin, septic sore throat is far more serious than brucellosis since the latter disease may originate in other sources than the bovine animal and its products.

The data in the following table are taken from the Public Health Reports of the United States Public Health Service:

Paratyphoid fever is not a clean cut example of a disease of animal origin. The paratyphoid fevers or Salmonelloses constitute a group of human infections due to a variety of species of *Salmonella*. Many epidemics and isolated cases are, like typhoid, spread from man to man directly or indirectly, while a few are certainly of animal origin. The term "food poisoning" may more aptly relate to the Salmonelloses of animal origin. For the year 1931 the Public Health Reports gave the following data on the occurrence of food poisoning:

California	398 cases
Ohio	147 cases
Kansas	1 case
	546 cases

No cases were reported from any other states. There is obviously no relation between the occurrence of food poisoning and undulant fever.

Comparative frequency of three diseases of animal origin, 1931.

State	Paratyphoid Fever	Undulant Fever	Septic Sore Throat
Alabama.....	0	14	0
Arizona.....	0	11	8
Arkansas.....	8	2	0
California.....	69	96	91
Colorado.....	14	31	17
Connecticut.....	33	19	114
Delaware.....	0	2	0
Florida.....	3	1	0
Georgia.....	27	6	440
Idaho.....	3	23	8
Illinois.....	36	127	120
Indiana.....	0	27	27
Iowa.....	3	48	8
Kansas.....	15	47	38
Kentucky.....	0	0	0
Louisiana.....	19	58	24
Maine.....	12	5	11
Massachusetts.....	1	16	231
Maryland.....	0	43	98
Michigan.....	0	19	325
Minnesota.....	1	60	0
Mississippi.....	0	3	0
Missouri.....	0	134	268
Montana.....	0	4	38
Nebraska.....	0	4	38
Nevada.....	0	0	0
New Hampshire.....	0	0	0
New Jersey.....	13	45	0
New Mexico.....	4	5	8
New York.....	97	196	374
North Carolina.....	27	0	153
North Dakota.....	0	6	1
Ohio.....	22	115	1061
Oklahoma.....	0	13	381
Oregon.....	8	11	52
Pennsylvania.....	0	39	0
Rhode Island.....	1	0	17
South Carolina.....	77	3	37
South Dakota.....	0	6	3
Tennessee.....	18	7	142
Texas.....	24	0	0
Utah.....	0	0	0
Virginia.....	0	16	0
Vermont.....	0	15	7
Washington.....	5	33	0
Wisconsin.....	0	36	0
West Virginia.....	3	0	0
Wyoming.....	0	0	7
Totals.....	543	1346	4147

Comparative frequency and case fatality of diseases reported in 1931 by the various States to the U. S. Public Health Service.

Disease	Frequency	Case fatality per cent
Chicken pox.....	228,836	0.03 to 0.07
Whooping cough.....	163,838	0.6 to 0.8 (U. S. P. H. S., 3.8)
Measles.....	161,175	0.2 (U. S. P. H. S., 0.94)
Mumps.....	125,784	0.02
Influenza.....	110,813	2.0 to 5.0
Scarlet fever.....	96,341	1.0 (U. S. P. H. S., 1.3)
Malaria.....	75,036	Low with proper treatment
Diphtheria.....	69,617	5.3 to 6.6 (U. S. P. H. S., 9.0)
German measles.....	33,100	Very low
Small pox.....	27,706	0.34 to 30.
Pellagra.....	27,152	3 to 4 to very high
Typhoid fever.....	24,963	8.3 to 12.5 (U. S. P. H. S., 20.0)
Poliomyelitis.....	15,698	14.0
Diarrhea.....	13,347	Low
Meningococcus meningitis.....	5,366	14 to 50
Septic sore throat.....	4,221	2.4 to 4.5 or lower
Hookworm.....	4,164	Low—direct mortality
Ophthalmia neonatorum.....	2,923	Low
Dysentery.....	2,833	Variable
Vincent's angina.....	2,107	Low
Trachoma.....	1,982	Low
Impetigo contagiosa.....	1,583	Low
Rabies in animals.....	1,384	100
Undulant fever	1,341	2 or less
Puerperal septicemia.....	936	High
Lethargic encephalitis.....	790	High
Dysentery amebic.....	705	Low
Paratyphoid.....	559	Less than 2 to 3.3
Tularaemia.....	553	Very low
Food poisoning.....	546	Very low
Scabies.....	520	Rarely fatal
Tetanus.....	484	Low with proper treatment, otherwise very high
Typhus fever.....	407	7 to 13.26 and higher
Diarrhea and dysentery.....	381	
Lead poisoning.....	278	May be high in acute cases
Diarrhea and enteritis (under 2 years).....	277	Very high
Dengue.....	215	Very low
Conjunctivitis.....	196	Very low
Rocky Mt. spotted fever.....	194	22.6
Trichinosis.....	190	4.0 to 16 or 30
Jaundice.....	98	Unusually low—some epidemics, high
Anthrax.....	65	20
Leprosy.....	39	Very high
Rabies in man.....	26	100 after disease develops
Actinomycosis.....	18	Low
Ptomaine poisoning.....	18	Diagnosis questionable

Disease	Frequency	Case fatality per cent
Granuloma, coccidioidal	16	Very high
Trench mouth	13	See Vincent's angina
Botulism	9	High
Silicosis	9	May be high
Milk sickness	7	High
Diarrhea and enteritis (over 2 years)	7	Low
Ludwig's angina	5	Variable
Relapsing fever	4	Low
Psittacosis	2	14 to 20
Sprue	2	High
Giardia enterica	2	Low
Tick paralysis	1	
Conjunctivitis infectious	1	
Thrush	1	Low
Beri Beri	1	Variable

Data on case fatality for diphtheria, measles, scarlet fever, typhoid, whooping cough, chicken pox, mumps, poliomyelitis and cerebro spinal meningitis from Harold B. Wood—Case Fatality of communicable Diseases. Jour. Preventive Medicine, Vol. 6. p. 87-93, 1932.

Data on case fatality of typhus fever—the Etiology and Pathology of Typhus, p. 17 from S. B. Wolbach, J. L. Todd and F. W. Palfrey. Harvard Univ. Press, 1922.

Data on case fatality for Rocky Mountain Spotted Fever—The Typhus-Rocky Mountain Spotted Fever Group. A. Rumreich, R. E. Dyer and L. F. Badger, Public Health Reports Vol. 46, p. 478, 1931.

The Surgeon General of the U. S. Public Health Service (1931, p. 217) in his annual report gives the following three-year averages for the number of cases for each death: Diphtheria, 11 to 1 (9 per cent); measles, 106 to 1 (0.94 per cent); scarlet fever, 78 to 1 (1.3 per cent); typhoid fever, 5 to 1 (20 per cent); whooping cough, 26 to 1 (3.8 per cent).

Gentry (1930) states that "The average case mortality (Undulant fever) in the British Army and Navy in Malta for seven years prior to 1908 was 2.3 per cent. In the civil population, however, for the same period the case mortality was much higher, 10.5 per cent". These data are furnished by Eyre (1908) (67).

Cause of the Disease

Brucella Melitensis—Horrocks (10) gives a good description of this microorganism based on his efforts to devise a better medium and tests for the differentiation of *Micrococcus melitensis* as it was then called:

Cultural Characteristics

Glucose peptone, 1 per cent, lactose peptone, 1 per cent, saccharose peptone, 1 per cent and starch peptone, 1 per cent: Growth. Neither acid nor gas produced.

Litmus milk: No clotting observed; at the end of three weeks the medium was found to have a distinctly alkaline reaction.

Peptone and salt solution: On the addition of a nitrite and pure sulphuric acid, the nitroso-indol reaction was never obtained.

Broth: Diffuse growth without any surface pellicle. After some days the broth cleared somewhat, and a deposit formed on the sides and at the bottom of the tube.

Agar slope: Greyish-white moist growth; discrete colonies, circular and trans-

parent, resembling those of Gram staining streptococci found in feces and urine. When the cultures are old, the growth often acquires a yellowish-brown color.

Proskauer and Capaldi's media No. I: No growth. No. II: Growth, but no change appeared in the reaction of the medium.

Neutral red: Unchanged after 48 hours at 37° C.; after five days' incubation a yellow color appeared at the surface.

Potato: Moist transparent film appeared, and on scraping the surface a copious growth was obtained, the formation of chains being very marked. The reaction of the potato was made faintly alkaline by the addition of sodium carbonate, and on planting out on the surface a distinct yellowish colored growth was obtained.

MacConkey's bile salt broth: Growth; reaction unchanged.

Nitrate broth: Growth, but no reduction of the nitrates occurred.

Gelatine stab and slope (22° C.): Growth extremely slow; no liquefaction of the medium.

Agar stab (37° C.): Diffuse growth.

Anaerobiosis: Growth, but more feeble than under aerobic conditions.

Morphology: Very small cocci, appearing as diplococci and short chains; occasionally chains of twelve to fourteen cocci were observed.

Brucella Abortus—The following description of Bang's bacillus is taken from the Report of the Departmental Committee appointed by the (British) Board of Agriculture and Fisheries to inquire into epizootic abortion, Professor John McFadyean, Chairman:

Morphology—If a suitably stained preparation made from the uterine exudate of an affected cow be examined under the microscope a large number of white blood corpuscles and catarrhal cells from the uterine mucous membrane can be seen. Between the cells there are numerous small single bacilli, which are mostly of an oval shape; some, however, are distinctly rod-shaped, like the tubercle bacillus, and show one or two unstained areas in their substance. In many places the bacilli are collected into dense groups or colonies. Some of these groups look as if they were bounded by a cell membrane, and give the impression of being contained inside tissue cells.* In many cases, however, they look simply like collections of agglutinated bacilli, an appearance which it will be afterwards seen they affect in artificial culture on certain liquid media. Lying amongst the smaller elements of a colony one sometimes sees very large oval elements which take the stain very deeply.

As a rule the majority of the bacilli are between one and two microns in length, but many are less than one micron. The longest measure about three microns.

The bacilli are non-motile.

Staining—They stain admirably with methylene blue or diluted carbol-fuchsin. They do not retain the stain when treated by Gram's method and they are not acid-fast.

Occurrence of the Bacilli in the Foetus and Its Membranes—In no affected uterus while fresh were abortion bacilli found in the fluids contained inside the foetal membranes. In the foetus itself, however, they were frequently, though not always found in the fluid contents of the stomach.

Abortion bacilli were found in the stomach fluid of the foetus ten times in nineteen experimentally infected cases that is, in 52 per cent * * * *

In the same 19 experimental cases in cattle the abortion bacillus was never found in the foetal heart blood, but on one occasion cultures were obtained from the heart blood of a lamb (see Appendix 1, F, Experiment 44, Ewe 58). On one occasion only was the bacillus found in the peritoneal exudate of the foetus (see Appendix 1, Experiment 1, Foetus 22).

In stained preparations from the mucus present in the foetal stomach one sees squamous and columnar cells shed from the mucous membrane. Large colonies of the abortion bacillus are seldom met within this material, but one may see considerable numbers of the single rod elements.

Cultural Characters—For the purpose of obtaining pure cultures the custom was to thoroughly sear the surface of the intact uterus, open into it with a sterilized

*In this connection it is pertinent to note the observation of Smith, Smith, Theobald—(1919). A characteristic localization of *Bacillus abortus* in the bovine fetal membranes. Jour. Exp. Med., Vol. 29, p. 451.

knife, and extract the exudate by means of a sterilized platinum scoop. It is from the exudate that the best cultures are obtained. One can, however, also obtain cultures from the contents of the foetal stomach. For the collection of the latter material the surface of the foetal stomach was seared, and its wall pierced by sterilized glass pipettes, into which the fluid was aspirated. Keeping in mind the characters assigned by Professor Bang to the bacillus isolated by him from affected cows in Denmark, we attempted in the first instance to obtain cultures on the artificial media—agar-gelatine + raw serum, and glycerine-broth + raw serum—which he stated to be essential for the cultivation and identification of his organism. According to Bang (3), when tubes containing agar-gelatine + raw serum are sown with uterine exudate, and incubated, one finds "at the end of from two to four days a great number of very small colonies, which develop only in a definite zone of the tubes. This zone lies half a centimetre (about $1/5$ inch) under the surface of the nutritive medium, and it has a thickness of from one to one and one-half centimetres ($2/5$ to $3/5$ inch). Colonies are not present either above or below this". Professor Bang (3) goes on to say in this connection, "We had thus not to do with an aerobic bacterium, which would have pushed its growth as far as the surface of the nutritive media, and still less had we to do with an anaerobic form, which would have grown as far as the bottom of the tube. The under-limit of the zone of growth lay exactly where the limit of the growth of an anaerobic bacillus shows itself (the necrosis bacillus, for example). This highly peculiar behavior of the abortion bacillus towards oxygen made it at once apparent that we had to do with a distinct species, and therefore rendered it in the highest degree probable that there was a causal connection between the bacterium and the disease."

"Obviously the peculiar mode of growth which has just been mentioned greatly facilitated our further studies, as we were thereby enabled to recognize the specific bacillus even when it was present in very impure cultures. The colonies are very small, even punctiform, the largest scarcely attaining the size of a pin's head. Their form is roundish, and when slightly magnified their edges seem to be finely dented."

When describing later the behavior of his bacillus in liquid cultures—glycerine-broth-serum (raw)—Bang (3) further stated that the growth could sometimes be rendered more luxuriant by bubbling a large quantity of oxygen through the fluid and afterwards sealing the mouth of the flasks. In speaking of the biological characters of his bacillus, he stated that his observations "appeared to show beyond any doubt that for the abortion bacillus in its behavior towards oxygen there are two optima—first, a degree of oxygen tension in the nutritive medium less than that of the atmospheric air; and second, the presence in the nutritive medium of a very high oxygen tension, which, however, lies somewhat under 100 per cent. Between these two optima there is an intermediate zone in which the abortion bacillus grows badly or not at all." Further, he stated that with the Danish bacillus the growth in glycerine-broth was meagre, and he apparently failed to obtain any growth on the surface or agar or on potato.

We have thought it necessary to quote the above description at length, because the cultural characters of the bacillus were stated to be specific, and to constitute a standard whereby one might recognize the organism of the Danish disease, and because failure to obtain the typical cultures above described when working the exudate found in the English disease was almost invariable. Further, the bacillus which was isolated and proved to be the cause of cattle abortion in England exhibited many other biological characters different from those described by Bang in connection with the Danish bacillus. Indeed, those differences were so material that, although we were convinced from the start that we had met in the uterine exudate, at least, with the same organism as that described by Bang in Denmark, resort had frequently to be made to experimental tests on pregnant animals in order to prove that the apparently different forms of organism which we had isolated in artificial culture were capable of producing abortion.

Agar-gelatine-serum (raw)—On agar-gelatine-serum (raw), it was almost immediately below the surface of the medium, or the first appearance of growth consisted of a large number of very small isolated grey specks in the thin film of medium on the surface at the circumference of the tubes. The grey sub-surface cloud very speedily spread to the top, especially if some liquid had been expressed from the medium in the cooling process. Very frequently, too, it was found that the first growth appeared in the expressed surface fluid, if such existed. Distinct macroscopic colonies only appeared in the sub-surface layer of the medium, that

is to say, below the greyish ring, after a week or more. Frequently, even when there was no surface fluid present, the growth would extend over the surface of the medium as a thick dirty-white layer. Moreover, it was found that certain microbes which were undoubtedly impurities would sometimes give a growth very similar to that described by Bang as occurring in this medium. Notably, did it occur to our astonishment that the tubercle bacillus isolated from the uterus of Cow 23 (see Appendix 1, A) gave a growth absolutely identical with that described by Bang as typical. In fact, from a pictorial point of view it was the most typical growth obtained. Again, it was found that a totally different microbe which was isolated from sheep in the field and which has been proved to cause abortion in that species, may, and frequently does, give a growth almost identical with that described as typical of the Danish bacillus of cattle abortion. * * * * *

This medium (agar-gelatine-serum) for various reasons was found difficult to manipulate, and as it did not seem to have any specific qualities it was discarded, except for the purpose of special observations (see Appendix 1, B). It was also discovered later that a solid medium with all the advantages, such as they are, and none of the disadvantages, of the above, could be prepared by adding to the agar-gelatine a similar proportion of serum which had been diluted, alkalinized, and sterilized at a high temperature. Tubes of solid media prepared in this way could be sterilized in the autoclave without the serum undergoing coagulation. In the solidified condition they can be kept in stock, and they can be liquefied when necessary by simply heating the tubes in a Bunsen flame.

The individual sub-surface colonies vary in size from a pin's point to the head of a large pin, but, of course, the larger ones develop at a later period. The smaller colonies are greyish in colour, but as they increase in size their centres become of a distinct rusty brown. In outline they are circular, and in many cases the margins are dentated. The most distinct character of the abortion bacillus grown in this way is the appearance of the larger colonies, which have a brownish centre, grey outer part, and dentated edge.

Agar—On the surface of agar excellent growths of the bacillus were obtained. In order to get such a growth from the uterine exudate one must incubate the tubes for 10 days or more, and for that reason the suitability of this medium was at first overlooked. One can, however, obtain excellent growths on the surface of agar in two or three days by sowing with the culture in the top fluid expressed on the agar-gelatine-serum tubes. After one or two changes from smear to smear these surface cultures grow more luxuriantly. At first the growth appears in the form of tiny dewdrops. If the material used for sowing has been only moderately rich in organisms, the colonies grow in an isolated manner on different parts of the surface. As they increase in size they develop a faint bottle-green colour, which after a time takes a distinctly yellow, and sometimes a brownish, tint. If the seed material has been rich in organisms a dewy film appears all over the surface. This film also takes on the faint bottle-green tint, and may become yellow or even brown, while a dense greyish deposit of microbes forms in the water of condensation at the bottom of the tubes. At first, as already stated, on account of the apparently great difference between this manner of growth and that of the microbe isolated in the case of the Danish disease, we were inclined to look upon these surface growths as contaminations. That they are cultures of the abortion bacillus cannot be doubted, however, as will be seen later.

Plate Cultures—Plate cultures can also be obtained on the above solid media contained in flat bottles, such as Soyka's flasks, by liquefying the material, allowing it to cool to between 40 and 45° C., sowing it with exudate or culture, shaking the material through the medium, and then allowing the latter to solidify while the flask is laid flat. For plate cultures, however, plain agar is not so suitable as the agar-serum mixtures. In plate cultures colonies of abortion bacilli appear first throughout the sub-surface layer like brownish-grey specks of bran, and as the colonies increase in size many of them show the reddish-brown centre, grey outer part, and dentated margin. In such flasks there is always a certain amount of condensation fluid. The growth may soon appear in this, and ultimately spread over the surface. Some of the sub-surface colonies extend to the top of the medium, and grow quite luxuriantly on the surface. For obtaining pure cultures of the abortion bacillus from contaminated material the plate method has not been found useful, because the bacillus grows much more slowly than most of the contaminations, and the latter speedily cover the surface of the medium, obscuring the abortion colonies or preventing their growth.

Gelatine—Gelatine was found useless for the cultivation of the abortion bacillus * * * *

Potato—At first it appeared as if potato was useless for the cultivation of the English bacillus, as it had apparently been found to be for the Danish organism. It is not easy to start cultures on potato from the exudate, but it was found to be a most excellent medium for obtaining sub-cultures. No growth, however, is apparent until it begins as a honey-coloured layer, which soon changes to a deep chocolate colour like that seen in cultures of the glanders bacillus. The bacillus of cattle abortion, then, is chromogenic. After a month the layer of growth is very dense.

Glycerine-broth + Raw Serum—This is the medium which was used for the purpose of obtaining liquid cultures of the microbe causing the Danish disease. Cultures of the bacillus which was isolated in connection with English disease were also obtained in this medium, but it was discarded, except for special observations, because of the difficulty of getting large quantities of serum in a sterile condition for culture purposes, and of the facilities which arise for the contamination of tubes and flasks when raw serum has to be added to them. It was found that if glycerine-broth be mixed in equal proportion with diluted alkalinized serum sterilized at a high temperature, one obtains an equally good and much more convenient liquid medium. Further, if 1 per cent of grape sugar be added to this medium the abortion bacillus grows much more luxuriantly than in any of the others previously mentioned. Flasks or tubes of this medium may be sterilized in the autoclave, and if sown with abortion bacilli and incubated under ordinary aerobic conditions a very luxuriant growth develops. The method of replacing the air in the flasks by bubbling filtered commercial oxygen through the liquid for a more or less prolonged period, and then sealing the neck of the culture flasks, does not increase the luxuriance of the cultures. The method, moreover, has many disadvantages. For example, it increases the facilities for contamination, and it renders the flasks liable to burst in the incubator after a period of incubation, because the abortion bacillus in the process of cultivation uses up oxygen, and creates a more or less considerable vacuum inside the flasks. Even if a flask be sown heavily in the ordinary way without replacing the air by oxygen, and the neck be sealed, there is considerable danger of its collapsing inwards owing to the absorption of oxygen by the bacilli from the contained air.

In the liquid serum medium the first growth appears in the form of a grey precipitate. Later on, little yellow and grey flocculi collect at the bottom of the flasks or tubes. The flocculi are more abundant in the raw serum mixtures, especially when sown with exudate.

Peptone-broth—This is not a good medium for obtaining a first culture from natural material, such as exudate, but a fairly good growth is obtained in peptone broth if it be sown with material from agar slopes. If 1 per cent of grape sugar be added to the broth the growth is greatly improved, but it is always inferior to that obtained in the glycerine-broth-serum mixtures sown in the same way. In broth made from liver it also grows fairly well.

Milk—Very good growths of the abortion bacillus were obtained in sterilized milk, but this cannot be considered a useful or convenient medium. Attempts were made, without success, to keep a culture of the abortion bacillus going inside the mammary gland of a milch cow. A pure culture can be injected up the teat of such an animal without causing mammitis, but it was not possible to find abortion bacilli in the milk a week after the infection had been performed.

Physical Requirements—The abortion bacillus grows best at temperatures between 30° and 37° C. One cannot start a culture outside the incubator, but if actively growing cultures on solid media be incubated for a few days, and then taken out, the growth seems to increase slightly at the temperature of the laboratory.

The bacillus is an aerobe, that is to say, it requires oxygen for its development. It will, however, grow fairly well in a rarefied atmosphere containing very little oxygen, but it will not grow under anaerobic conditions. In fact, one can destroy the vitality of an active culture by putting it in the incubator at 37° C. under anaerobic conditions for two or three days.

Microscopical Appearance of Cultures—The microscopical appearance of cultures varies greatly, according to the medium from which the preparation has been made, and the seed material from which the culture has been obtained. In preparations

made from media containing a large proportion of raw serum (one-third) one finds the microbe growing in clumps, no matter what material has been used for sowing, giving an appearance which might be described as that of staphylo-bacilli. The clumping is particularly evident when the medium has been sown directly with uterine exudate. Some of the clumps in the latter case may be seen to contain as many as a hundred elements.

Through the kindness of Professor Bang we have on several occasions received liquid cultures (in raw serum media) of the Danish bacillus from his laboratory for comparison. These always showed small clumped forms, and at first gave the impression that this was the specific form of growth. If preparations be examined from the heated liquid serum media the appearance is the same, provided the culture has been obtained by sowing heavily with natural material. It is otherwise, however, if sub-cultures on heated serum be made from the first culture, or if the flasks be sown from agar smears or other cultures on solid media. In this case one sees nothing but single bacilli, which very much resemble the individual elements of the clumps, but no clumps are present. In hanging-drop preparations no movement is observed. If preparations be made from agar smears or from the top growth on agar-gelatine-serum (heated), only single elements can be seen, and no clumps are present, although of course, in such preparations the organisms may be densely packed.

These distinct departures from the characters described as typical for the bacillus of the Danish disease again suggested that possibly a different microbe, and one which was not the cause of abortion at all, had been isolated. It was found, however, that if the raw serum medium was inoculated from an agar slope or other clumpless culture the bacillus grew again in the clumped form. Moreover, if raw serum was added to a clumpless liquid culture in sufficient quantity (about one-third of its bulk), the latter after standing was transformed into a typical clumped culture, and it seemed highly probable that the clumped appearance of the cultures in raw serum was simply due to the natural agglutinating power of the serum. This agglutinating power was, of course, destroyed by the sterilizing temperature, with the result that the organism grew in the unclumped form in the heated serum medium. The exudate, however, also contains agglutinating substances, as may be gathered from the clumped appearance of the organisms in the exudate obtained directly from the uterus, and when heated serum is heavily sown with this material it gives rise to agglutination or clumping of the bacilli.

* * * There seems no reason to doubt, then, that the Danish and English diseases are one and the same, and we have not thought it necessary to coin a name for the bacillus, as it seems appropriate that it should be known as "Bang's Bacillus of Cattle Abortion" in deference to the work of its distinguished discoverer.

Thermal Death-point—* * * It was found that in the moist state it was not destroyed at a temperature of 55° C. maintained for an hour, but two hours at the same temperature proved fatal. If it be kept for ten minutes in water at a temperature between 59° to 61° C. and above, its vitality is destroyed, but after exposure in water at 55° for ten minutes it retains its vitality.

Formation of Toxins—When the bacteria were removed from an actively growing culture by filtering through a Chamberland filter it was found that one could inject large doses of the filtrate into animals without giving rise to any notable disturbance.

Apparently there is no appreciable formation of soluble toxins in the cultures. When an animal is inoculated, however, with a comparatively large amount of liquid culture or exudate a distinct febrile reaction may follow in a few hours. Occasionally distressing symptoms of dyspnoea may follow immediately. Such symptoms are more likely to arise when an animal is inoculated for the second time after an interval of about ten days. Apparently, then, toxins are developed, but they are of the nature of endotoxins, that is to say, they are contained inside the bodies of the bacilli. Moreover, it would appear that the toxins are not completely destroyed by a high temperature (100° C.), since the inoculation of a sufficient dose of bacilli so heated may cause a febrile reaction in affected animals, and even in normal ones, but to a less extent.

Brucella Suis—The first description of this organism having any degree of completeness was by Good and Smith (7). They studied the microbe isolated from a natural infection in swine in Kentucky:

Cultures from the internal organs of the fetuses, however, were nearly sterile. The clear places on the plates were marked with India ink, after which they were subjected to the cultural method of Nowak.* The material was incubated at 37° C. for four days and removed from the jars. On casual examination of the petri dishes, we were led to believe that they contained nothing but the growth of bacteria usually encountered in plating material which had lain on the ground for some hours. Upon examining one of the plates carefully with a Coddington lens, however, there were noted in some of the clear spaces of the dishes a few very small dew drop like colonies, which on being examined with the microscope resembled in every respect colonies of the *B. abortus* of Bang. Examined by the aid of the hand lens they were nearly water clear to direct light and of bluish tint to reflected light. They were round and raised, with exceptionally well defined borders. Most of these minute dew drop colonies were homogeneous, with the exception that a few of them had a few granules in the center, typical of many colonies produced by the *B. abortus*. Viewing the larger colonies under the microscope, it was seen that the centers had assumed a granular consistency, while the outer portion was homogeneous and transparent. The colonies on some of the plates were so large that they might have been taken for some other species, measuring 13 $\frac{1}{2}$ mm. in diameter. These conformed, however, to similar colonies of *B. abortus* derived from the tissues of the cow. To reflected light they had assumed an amber color, the centers having a whitish appearance. On examining stained preparations of these colonies, the morphology of the organism was identical, so far as we could determine, with *B. abortus*. On examining the plates carefully with a Coddington lens and microscope, colonies resembling those mentioned and measuring from a pin-point to 1.5 mm. in diameter were seen on streaks made from the blood of the umbilicus, on the streaks made from the small nodule-like growths on one of the afterbirths, and from the afterbirth and internal organs of the fetuses. Eighty-four colonies in all were counted on streaks made from one of the small nodules. Some of these colonies were so small that they could not have been seen with the naked eye. There were one or two colonies on the streaks made from the livers. The plates streaked with the amniotic fluid were almost completely covered with contaminating bacteria, but, in the clear spaces five dew drop colonies were noted. The streaks of the contents of the stomachs of both pigs showed numerous small dew drop colonies. Streaks from the kidneys were negative. Stained preparations had been made from the different organs mentioned but were not examined until the cultures had developed. Upon examining these preparations, germs identical with the *Bacillus abortus* (Bang) were seen in large numbers in those made from the stomach contents of the pigs.

Typical colonies were streaked on agar slants, some of which were incubated by the Nowak method and others in the air. At the end of twenty-four hours, no visible growth was noted on the streak cultures incubated in the air. At the end of forty-eight hours, however, some little growth could be detected even with the naked eye, and at the end of seventy-two hours, quite a luxuriant growth of the organism was obtained, in appearance identical with streak cultures made with the *B. abortus*. On examining the tubes which had been incubated under the Nowak method, we found that they had made but slightly better growth than those incubated in the air. Streaks on agar at room temperature showed no growth in the time mentioned. We came to the conclusion that if this organism was the *B. abortus* and grew in the air after the first generation it was different from any we had ever isolated. The organism responded to the following tests in the following manner. It was found to be non-motile; gram negative; did not produce gas in either lactose or glucose; did not coagulate milk; grew readily in plain bouillon, showing a fair degree of cloudiness at the end of seventy-two hours; and did not liquefy gelatine. Serum-agar tubes heavily inoculated with this organism and quickly solidified in ice water and incubated in the air, developed a growth characteristic of the *B. abortus* as noted by this laboratory, in that a narrow ring of growth appeared as a slight haze three mm. beneath the surface of the medium at the end of sixty hours, and eventually extended to the top of the medium. All the above tests conform to the biological and cultural characteristics of the Bang bacillus.

We were not, however, satisfied that the organism isolated was the *Bacillus abortus* on account of its growing in the air so readily, so we subjected the culture to the agglutination and complement fixation tests, using the serum from a rabbit made immune to the Bang bacillus, which agglutinated in high dilutions. It was found that this serum agglutinated our organism in a dilution of 1:1200, which was exactly the same dilution in which the serum agglutinated an antigen made of a well known strain of the *B. abortus*, which had been obtained from an aborting cow. Using as an antigen the organism isolated from the sows and the immune serum mentioned, the complement

*Nowak, J. Lebacille de bang et sa biologie. Ann. de l'Inst. Past., 22 (1908), p. 541.

was completely fixed with 0.02 cc. of serum. We were thus convinced that this organism was identical with the germ that produces abortion in the cow, the only difference being that it grew readily in the air after the first generation, while the cultures we have derived from the cow usually do not grow in the air until after being cultured for several generations by the Nowak method.

Brucella from Other Animals All the available evidence is that the *Brucella* from man, sheep, horse, poultry, dog, or any other animal is one of the three species: *Brucella melitensis*, *Brucella abortus*, or *Brucella suis*.

Differentiation of the Species of *Brucella*

It requires only a casual reading of the descriptions of the morphological and cultural characteristics of the three species of *Brucella* by Horrocks (10), by the British Departmental Committee (26), and by Good and Smith (7) to cause one to incline toward the idea of difference rather than identify with respect to these microbes. Certainly it had not occurred to Horrocks or to the members of the Committee that there was any relationship between the "micrococcus" of Bruce and the "bacillus" of Bang. Even Good and Smith noted that the microbe isolated from swine was essentially different in its atmospheric requirements from the bacillus of Bang with which they tried to identify it. It was the epoch-making researches and conclusions of Evans (5) that brought to the attention of students of this group of diseases the undoubted fact that there is a relationship between *Micrococcus melitensis* and *Bacterium abortus*. (See pages 10-12.) However, further study of the entire group of microbes convinces one that there certainly is not identity or a degree of relationship sufficient to warrant subjecting some of them to a subordinate position of *varietas*.

The work of Huddleson (8) and his associates has made it clear that there are three distinct species of *Brucella*,—*melitensis*, *abortus*, and *suis*—related generically but specifically distinct.

Morphology—Duncan (68) finds that young growing cultures on a rich medium such as Fildes' blood-digest-agar actually show distinctive morphology, the *abortus* developing bacillary forms and the *melitensis* coccil forms.

Biological Properties—Huddleson (70), (71) first demonstrated that Bang's bacillus requires for primary isolation, and is upon further subculturing stimulated by growing the cultures in an atmosphere of ten per cent CO_2 . At the same time Stafseth (72) proposed the use of liver infusion medium which has proved to be superior to any other basic medium. Huddleson (70) found that the H-ion concentration of the medium is an important factor, the optimum being pH 6.6 to 6.4. He also added to our knowledge of primary cultivation by pointing out that by incorporating a saturated aqueous solution of gentian violet in medium in sufficient quantity to give the dye a final dilution of 1-200,000, the growth of a large per cent of organisms occurring in milk other than *Brucella abortus* may be suppressed. This applies also to other materials for culturing. The results are approximately as accurate as those from guinea pig inoculation.

Wilson (1931) (74) believed that for growth to occur with *abortus*, both CO_2 and oxygen are required; the optimal concentration for the former is 5 to 10 per cent and for the latter 20 per cent. A lowered oxygen pressure is less favorable than the atmospheric oxygen tension. He concluded that the carbon dioxide promotes growth not by altering the acidity of the

medium but by diffusing rapidly through the intact cell wall and giving rise to an increase in the intracellular H-ion concentration of the cell.

Huddleson (73), first called attention to hydrogen sulphide production as a means of differentiating the species of *Brucella*. If a strain continues to produce H_2S to a considerable degree for a period of four days, it is *suis*; for a period of only two days, it is *abortus*; when no, or only a trace of, H_2S is produced in this period it is *melitensis*. Favilli (75) believed that H_2S production is the most trustworthy method known for distinguishing the species. Severi (76) found that H_2S was developed by 24 out of 77 *abortus* strains, whereas only 3 out of 17 strains of *melitensis* developed H_2S . Repeated passage through guinea pigs failed to alter their properties.

Huddleson (8) has reviewed the literature and presented his own findings on the growth requirements of *Brucella*. He summarized his results and concluded as follows:

"A total of 310 strains of the genus *Brucella* have been studied to determine the accuracy of a rapid and simple method of distinguishing the main species to which they belong.

"It has been found that by taking advantage of their behavior toward dyes in suitable dilutions in a medium, all strains fall into one or the other of three groups or species.

"Those strains which are slightly, if at all, inhibited in their growth on beef liver infusion agar containing thionin in a 1-25,000 or 1-50,000 dilution or containing basic fuchsin in a 1-25,000 or 1-50,000 dilution belong to the *Br. melitensis* species.

"Those strains which grow on the thionin medium but fail to grow on the basic fuchsin medium belong to the *Br. suis* or porcine species.

"Those strains which grow on the basic fuchsin medium but fail to grow on the thionin medium belong to the *Br. abortus* (Bang) species.

"By employing a medium containing thionin in the dilution mentioned and one containing basic fuchsin in the proper dilution, the three known species of *Brucella* can be distinguished from one another.

"On the basis of the present existing evidence, it is proposed that the genus *Brucella* be divided into three main species, namely, *Br. abortus* (Bang), *Br. suis* (Traum), and *Br. melitensis* (Bruce)."

Huddleson (73) now recommends that the dyes be prepared in a 1 per cent stock solution or suspension in distilled water. The final dilution which should obtain for thionin is 1-50,000 to 1-75,000 and for basic fuchsin 1-25,000. At the end of the period of incubation of plates one will find that strains of *abortus* have grown only on the medium containing basic fuchsin; those of the *suis* species have grown only on the medium containing thionin; the *melitensis* strains have grown on both of the media.

After more than a year of further study, Huddleson (69) reported again on this same subject:

"A total of 656 strains of *Brucella* from Europe and North America have been studied in their growth behavior toward aniline dyes in a suitable medium.

"It has been found that these strains divide themselves into three groups or species according to the growth inhibiting action of thionin in a final dilution of 1-30,000 pyronin in a final dilution of 1-200,000 in beef liver infusion agar at a pH of 6.6.

"Of the total number, 133 have been classified as *Br. melitensis* (Bruce), 352 as *Br. abortus* (Bang), and 172 as *Br. suis* (Traum). *Br. melitensis*

grows on both the thionin and pyronin dye medium, while *Br. abortus* grows only on the one containing pyronin and *Br. suis* only on the one containing thionin.

"The strains of *Br. abortus* may be divided into two classes: those which completely reduce basic fuchsin (final dilution 1-25,000 in beef liver infusion agar), and those which slightly reduce this dye. It appears, on the basis of isolated cultures, that the latter class is the one that is pathogenic for man.

"When more than one species of *Brucella* occurs in blood culture or other infective material, the dye method and H_2S metabolism determination will separate and identify each of the species.

"The growth inhibiting action of these dyes, especially pyronin, offers possibilities in the therapeutics of undulant fever in men and *Brucella* infection in animals."

Evans (77) found that it is possible to differentiate *Brucella melitensis* from *Brucella abortus* by the method of agglutinin absorption. Francis (1931) (78) effected an exchange of cultures with Dr. I. Forest Huddleson of our laboratory in an effort to test the validity of the claims for the agglutinin absorption test. He concluded that certain *Brucella* cultures, requiring carbon dioxide for their isolation, gave the *melitensis* A (Evans classification) serological reaction of *Brucella melitensis*, thus showing that agglutinin absorption is not a reliable test for the differentiation of *Brucella abortus* of Bang from *Brucella melitensis* of Bruce.

Zdrodowski et al. (1930) (59) found that serologically some strains of *Br. melitensis* were differentiated from *Br. abortus* while others were not. The serologically non-differentiated type of *Br. melitensis* was found to be the rule of Azerbaijan, although sheep and goats are the chief reservoir for human infection. Typical strains of *Br. paraabortus* were clearly differentiated, but a labile strain of *Br. melitensis* or *Br. abortus*, assuming the "para" characteristics, would acquire the serological characteristics appertaining thereto. These authors believe that Evans' proposal to classify the *Brucellas* by serologic characters is arbitrary.

McAlpine and Slanetz (1928) (79) concluded that the name *Alcaligenes* is a misnomer since all the members of the *melitensis-abortus* group can use sugars as a source of energy. They divided the strains studied into two groups: All strains that are unable to use more than two per cent of available glucose and all strains that can use from 5 to 20 per cent of the carbohydrate. In the latter group they place all strains of *Br. abortus* of human and porcine origin and *Br. melitensis*. They found one bovine strain that could use from 9 to 10 per cent of available carbohydrate. This, they thought, might be a porcine strain and they also thought that all of the human strains were apparently more closely related to porcine strains than they were to those of bovine origin. In this connection, it is interesting to note that Huddleston (1931) (69) calls attention to the fact that strains of *Br. abortus* may be divided into two classes: those that completely reduce basic fuchsin and those which slightly reduce this dye. It appears from his reports on the basis of isolated cultures, that the latter class is the one pathogenic for man. *Br. suis* is not active in the reduction of fuchsin. It would be interesting to check this culture by the sugar fermentation test of McAlpine and Slanetz.

Plastringe and McAlpine (1931) (80) identified 136 strains of *Brucella* of bovine, porcine and equine origin by the dextrose utilization method and by the dye plate method. Eight of 60 strains of bovine origin isolated in the

United States were found to be the porcine, and 52 of the bovine type. Of 56 strains of bovine origin isolated in Europe, 48 were of the bovine type and two appeared to be of intermediate type. All of the 22 strains of porcine origins were of the porcine type. Four strains of equine origin proved to be of the bovine type.

Plastringe and McAlpine (1932) (81) obtained data on 142 strains of *Brucella* of human, bovine, porcine, and equine origin. A comparison of the identity of these strains, as determined by their ability to utilize dextrose and their behavior on Huddleson's dye plates, with their serological characteristics shows that the agglutinin-absorption test failed to differentiate between *abortus* and *melitensis* so far as 23 per cent of the strains was concerned.

Kristensen (82) found that agglutination and agglutinin absorption experiments showed no type distinction between strains of *Br. abortus*, *Br. melitensis*, and the Danish swine type. The methyl-violet-thionin test and that based on H_2S formation appeared to give a good basis for classification of the group. By both of these tests, all Danish cattle and human strains gave reactions described as characteristic for the bovine type. Danish swine strains by methyl-violet-thionin test showed closest relations with the American swine type, from which, however, they differed through lack of H_2S formation.

Weigmann (1931) (83) confirmed Huddleson's findings with respect to the bacteriostatic action of dyes and pathogenic action of *abortus* and *melitensis* for monkeys. Agglutinin absorption tests failed to differentiate between old laboratory strains of these two species. *Melitensis* was found to be more resistant to the bactericidal action of normal human serum than *abortus*. By treating white mice with killed vaccines of either type, protection against infection with both homologous and heterologous types was demonstrated. The intracutaneous reaction was the same with both types of antigen (abortin and melitensin) regardless of which strain was responsible for the infection. No symptoms were produced in goats by inoculation with *abortus* either subcutaneously or per os. The organism could be recovered only from the inoculation site and it was not changed to the *melitensis* type. Guinea pigs, monkeys, and goats injected experimentally developed agglutinins and complement fixing antibodies in a titer equally high for *abortus* and *melitensis* strains. An *abortus* strain isolated from the blood of a human patient could not be differentiated from bovine strains.

Meyer and Zobell (84) used a semisolid low protein medium in tubes inoculated with a definite number of cells and found that 444 cultures of *Brucella* were tentatively classified into three general groups according to their tolerance to thionin, fuchsin and pyronin. While the H_2S test used alone has little differential value according to these workers, when used in conjunction with the dye tolerance tests, the ability to produce H_2S subclassifies the *Brucella* group into three major and three minor subgroups. They report that the representatives of *Brucella* reduce nitrates to nitrites in a semisolid medium containing 0.2 per cent KNO_3 . The nitrites are also rapidly reduced. The *abortus* and *suis* strains exhibit pseudo-anaerobic growth throughout the nitrate medium, while the *melitensis* strains grow in a zone a few millimeters below the surface. The *suis* strains destroy 0.05 per cent KNO_3 in five days while *abortus* and *melitensis* strains lack this ability. In media containing 0.2 per cent each of KNO_3 and KI, the *suis* types evolve an abundance of nitrogen gas with a rapid disappearance of nitrates and nitrites, while the *abortus* types very rarely liberate gas under

identical conditions. The *melitensis* and Danish porcine strains, although capable of destroying 0.002 per cent KNO_2 failed to generate gas. They found no significant difference between the various strains of *Brucella* in the utilization of dextrose or in the terminal reactions after growth in dextrose media.

Walton (1932) (85) tested 11 strains of *suis* and nine of *abortus* by both agglutination and complement fixation and found that reaction curves ran parallel in all cases. He concluded that they are identical as far as serological manifestations are concerned.

Brotzu (1930) (86) studied strains of *Brucella* from three sources: bovine strains from districts where undulant fever did not exist, strains from goats in regions where undulant fever was endemic, and porcine strains. He found no test which would distinguish the groups with certainty. He considered that bovine strains are pathogenic for man only if resistance is lowered, if the inoculating dose is heavy, or if the strain is relatively virulent, as, e. g., if it has been recently transferred from goats to cattle.

Cerruti and Sollai (1931) (87) isolated five strains of *Brucella* in Sardinia, two of caprine and three of sheep origin. Except that the two goat strains were not agglutinable with *abortus* and *melitensis* serum, all five strains showed the morphological, cultural, biological, and biochemical characteristics of *Brucella*. The two goat strains inoculated into rabbits had very weak antigenic power. Several strains of *abortus-melitensis* used for cross agglutination tests were found to be non-sensitive, or nearly so, to agglutination by homologous sera. The authors classified the caprine strains under *paramelitensis* and the sheep strains under *melitensis*.

Mallmann and Gallo (1931) demonstrated the value of phosphate media for the growth of *Brucella* and concluded that *Br. melitensis* and *Br. abortus* gave the same results as *Br. suis* in glucose infusion broth so far as utilization of the sugar is concerned.

The differentiation of the species of *Brucella* has received its full share of attention. Among the efforts directed to this end may be included those on pathogenicity studies. Huddleson and Hallman (88) (1929) profited by the work of Fleishner, Vecki and Shaw and of Burnet when they tested *melitensis*, *abortus* and *suis* pathogenicity on monkeys. They found that *abortus* was clearly pathogenic for the monkey (*Macacus rhesus*), in which it produced a disease resembling undulant fever. Infection, however, was not readily produced and in many cases did not occur at all. Monkeys were found to be very susceptible to infection from small doses of *suis* species regardless of its source. In fact their data indicated that *suis* is more virulent for the monkey than is *Br. melitensis*.

Practically all the available data indicate that man is susceptible to all three species of *Brucella*. A culture from man may be of caprine, bovine, porcine or ovine origin. There is no necessity for believing that a culture of bovine origin pathogenic for man is necessarily a porcine strain. Hardy et al. (1930) (31) found both *abortus* and *suis* in blood cultures from a fatal case, a farmer. Jordan and Borts (1931) (89) isolated both *melitensis* and *abortus* from a Mexican laborer. Both Huddleson and Francis corroborated the findings of the latter authors with respect to the identification of the cultures isolated.

The Dissociation of the Species of *Brucella* has been reported by a number of workers. Mallmann and Gallo (90) have reviewed the work

done on this subject and reported on their own extensive researches. The work is being continued under the direction of the senior author. It seems to be important that one should know the phase of dissociation of the organism that is being used for serological, immunological, biological or systematic study. Pure R strains seem to be constant in respect of biochemical, cultural and antigenic properties. The OS type, which appears to be in the early stages of impressed dissociation and to have been mistaken for the true R type, is probably an intermediate type and identical with the much-referred-to paramelitensis type. Taking these points of view into consideration the work of Mallmann and Gallo explains the failure of certain workers occasionally to confirm Huddleson's work on differentiation of the *Brucella* species by the use of dyes.

Rough forms of *Brucella* were obtained by aging on liver infusion agar slants followed by further aging in nutrient veal broth. The rough forms of *Brucella* studied behaved like pure-line rough strains of the paratyphoid group. Classification of S forms of *Brucella* by dye plates and hydrogen sulphide production does not hold for rough forms. Rough forms of *Brucella* were reverted to S type by passage through guinea pigs. The value of typing S forms of *Brucella* by dye plates and hydrogen sulphide is affirmed by the return of R types to their original groups by these two methods.

Already, (1930) (91) Marshall and Jared had studied dissociation of the *Brucella* group. Wilson and Miles (1932) (92) found both rough and smooth strains of *Brucella*. They reported that the smooth strains, comprising *abortus* and *melitensis*, were non-thermo-agglutinable, and though sometimes agglutinated slightly by acid, were not agglutinated by NaCl. The rough strains, comprising *para-abortus* and *para-melitensis*, were thermo-agglutinable, were agglutinated strongly by acid and not infrequently by NaCl. In their typical forms smooth and rough strains had no serological relationship, though intermediate strains occurred containing both smooth and rough antigen. By the use of sera prepared against absolutely smooth strains, it was possible by agglutinin absorption technic to divide the smooth members into two types, one type containing *abortus* and the other type containing *melitensis* strains. It was probable that the distinction between *abortus* and *melitensis* strains is due, not to the presence of quantitatively different antigens, but to the different quantitative distribution of two common antigens. Provided due regard was paid to the relationship between the absorbing dose and the titer of the serum, monospecific sera could be prepared in which the major agglutinin of the type alone persisted. The writers think that by means of these sera unknown strains of the *Brucella* group could be rapidly typed by direct agglutination. They did not study the rough strains fully, but it appeared that there was at least one antigen common to all *para-abortus* and *para-melitensis* strains.

It is to be expected that aberrant and atypical strains of *Brucella* will be encountered not infrequently.

Gilbert (1930) (93) found prevalent in Palestine a strain of low virulence from the lower animals and apparently occupying an intermediate position between *melitensis* and *abortus*. Assuming agglutination tests to be a criterion of infection, sheep and goats appeared to be the common carriers.

Harms (1932) (94) isolated, from the aborted fetus of a heifer, an organism identical with bovine strains in that it required several successive

cultures before it adapted itself to aerobic growth. In all other tests, it was identical with *Br. suis*.

Mallmann (1930) (95) attempted to locate some of the generic relations of *Brucella* (Alkaligenes). Cross agglutination tests indicated that the Genus *Pasteurella* and the Genus *Pfeifferella* are agglutinogenetically related to *Brucella*. Huddleson (1931) (69) noted a possible relationship between *Pfeifferella* and *Brucella*. "One particular organism which - - - could be easily confused with *Br. suis* is *Pfeifferella mallei*. The natural host of this organism (the latter) is the horse. So also is *Br. suis* sometimes found in the horse. The lesions produced in the guinea pig by both organisms through subcutaneous or intraperitoneal inoculation are not entirely unlike in character. Both attack the same organs, producing large necrotic abscesses, and cause abscess formation of the joints of the extremities. *P. mallei* is agglutinated by serum prepared against *Br. suis*, and *Br. suis* is agglutinated by a *P. mallei* antiserum. The reducing activity of *P. mallei* for dyes differs from that of *Br. suis* in that it gives a luxuriant growth on a medium in the presence of either thionin, basic fuchsin or pyronin. *P. mallei* is also a very active H_2S producer. This gas is produced in large amounts over a period of 10 to 15 days' incubation and determined by lead acetate paper. *Br. suis* produces very little H_2S after the 4th day of incubation. Cultures of supposed *Brucella* or *P. mallei* from horses should be examined very carefully by laboratory methods in order to avoid an erroneous classification which later might be disastrous."

Schofield (1931) (96) found that cattle vaccinated with commercial hemorrhagic septicaemia bacterins made from *Pasteurella* failed to react in a dilution as low as 1 to 25 to *Brucella abortus* antigen.

Francis and Evans (1926) (97) found that a large percentage of serums from human cases of tularemia reacted to the agglutination test for both *Br. abortus* and *Bact. tularense* (*Pasteurella tularensis*). They found that to a less degree *Brucella* sera agglutinated *Bact. tularense*. Agglutinin absorption tests suffice to separate the two infections.

Kamada (1931) (98) made comparative agglutination studies on the Bang bacillus, *B. typhi*, *B. paratyphi* and *B. dysenteriae* Shiga or Flexner, using 200 sera from parturients and gravidæ (last stages). Sera from women advanced in pregnancy produced agglutination of Bang bacilli in a significant number of cases; but these sera also very frequently agglutinated other bacteria. Therefore, (also because the sera frequently gave negative complement-binding reaction with *Br. abortus*) the agglutination would appear to be non-specific (not produced by antigen-antibody reaction). It was very easy to produce strains of *Br. abortus* divergent culturally, microscopically and serologically; but the virulence and immunizing action of these altered strains for guinea pigs, rats and white mice was unchanged. Immunity against infection was not attainable, but the fever following subcutaneous or intraperitoneal infection in guinea pigs could be prevented by immunization with suspensions of killed bacteria. Most of the artificially altered strains showed a tendency, after several passages in vitro, to revert to the original strain; reversion was frequent also in the bodies of infected animals. No infection of the fetus by the mother occurred in guinea pigs infected during the latter half of pregnancy, and no excretion of Bang bacilli in the milk was observed.

III. THE SOLUTION

1. Diagnosis of brucellosis hominis.
2. Clinical, history and epidemiology.

From the researches of Huddleson and others, the conclusion is made that there are at least three species of *Brucella melitensis*, *abortus* and *suis*. There is available sufficient evidence that each of these organisms is pathogenic for man and that each actually does cause infections in man in various parts of the world, one being responsible for brucellosis in one geographical section and another in another section or that more than one species may be responsible for human infection in a given locality. It may be *melitensis* and *abortus* in Mediterranean countries and the south-western states of the United States or it may be *abortus* or *suis* in Iowa and other states of the so-called corn belt or hog raising section. As already pointed out, two species may be isolated from the same human patient.

A study of the literature and experience with actual cases of the disease convinces one that brucellosis of man, wherever it is encountered and regardless of the species of *Brucella* that cause it, is practically the same disease in all countries. Thus Bieling (1930) (99) concluded that while morphology, cultural methods, comparative agglutination of the various strains with monovalent sera, etc., furnished no trustworthy criterion for distinguishing human and bovine *Brucella* strains from central Europe and from the eastern Mediterranean basin, the author's agglutination-binding method, especially applied to supervalent sera, enabled him, in tests on 28 human and 27 bovine strains of various origin, to distinguish two great groups: (1) the Mediterranean human type, and (2) the Central European bovine type. He found however that both types might infect either men or animals; and, no matter what the type of infecting organism, human infection presented the picture of undulant fever; the animal disease that of infectious abortion. It is improbable that the Mediterranean type occurs in Germany and adjacent countries. In Bulgaria, it predominates among human infections, while the German bovine type dominates among animal infections. In Palestine, the Mediterranean type seemed to be solely responsible for human infection, but the German bovine type occurs among cattle, especially in imported animals.

The disease has been described by Hughes, by Hardy et al., by Simpson and by Gentry. The description of the five clinical types of the disease by Lt. Col. Gentry (100) is reproduced in full because it embodies all that has been contributed by the principal workers in this field including the important clinical observations of Gentry himself. While the clinical diagnosis of undulant fever is difficult and in many cases impossible, the practitioner or the epidemiologist must have in mind the clinical picture, uncertain and vague though it may be.

Clinical Types of Undulant Fever

Hughes, from a careful study of the pyrexial curves of his large series of cases, differentiated three main types of the disease, malignant, undulatory and intermittent, although irregular and mixed types also were seen frequently. To the classification of Hughes, Bassett-Smith would add two additional types, ambulatory and mild forms. Eyre differentiated three types, acute, subacute and chronic, according to the severity of the disease, although he recognized these distinctions to be purely arbitrary.

1. **Ambulant Form**—These cases were recognized first by Shaw. Symptoms may be entirely absent, or are limited to a few days of slight fever. These cases are unrecognized unless sought for by examination of the blood for specific agglutinins or for the presence of the organism. These patients may, however, excrete virulent organisms in the urine in large numbers over long periods of time and are potential sources of infection.

2. **Mild Form**—These are frequent and often unrecognized or may be confused with malaria or paratyphoid fever. There may be a feeling of lassitude, headache, constipation, indigestion, thirst and slight sweating with a slight irregular fever lasting from a few days to two weeks. The temperature rarely rises above 102° F., falling one or two degrees in the morning and is usually of an irregular remittent character. With the return of the temperature to normal, convalescence rapidly follows.

3. **Undulatory Form**—This is the most common form, especially in *Brucella melitensis* infections. Hughes has well described its characteristic febrile course as "marked by intermittent waves or undulations of more or less remittent pyrexia, of variable length, separated from one another by periods of temporary abatement or absence of symptoms". This repeated alternation of waves of pyrexia with periods of normal or nearly normal temperature has given to the disease its name of undulant fever. The onset usually is insidious. For some days there is an ill-defined feeling of malaise with lassitude, anorexia, slight headache, thirst and constipation. The individual is depressed; there is increasing nervous irritability and insomnia. Muscular pains, described as "rheumatic," often are felt in back, neck and limbs, and a slight evening rise of temperature occurs, associated with chills. Less frequently, the onset is more abrupt, with acute fever, gastric irritability and sore throat. As a rule, however, the temperature rises gradually, remitting each morning about half the amount of the rise of the previous evening, until an elevation of 103°-105° F. is reached. The step-like character of the ascent resembles that of typhoid, but the prostration, apathy and toxemia of typhoid are wanting. Indeed, in the early stages of undulant fever, the patient often exhibits a singular lack of discomfort, which is most unusual in view of the height of the pyrexia. He endeavors for a time to carry on his usual occupation, but eventually is forced to desist. The headache, usually frontal, increases; the tongue is coated, moist, swollen and indented laterally; the breath is offensive; there is apt to be epigastric or perisplenic tenderness, and the bowels become markedly constipated. There is often bronchitis or hypostatic congestion of the lungs, in proportion to the severity of the case. Each remission of temperature almost invariably is followed by profuse sweating. There is increasing debility, and restlessness and insomnia become more marked. After a variable period, lasting from ten days to three weeks, there is a gradual decline of temperature corresponding to the ascent, until normal, or nearly normal levels are reached. With the decline of the fever, there is marked amelioration of all symptoms, and the primary wave of pyrexia is now over. The patient may wish to get up, but if he does so, a severe relapse promptly follows. After a few days of approximately normal temperature the characteristic pyrexia returns, and a relapse similar to the primary attack occurs, although usually less prolonged and less severe. This in turn subsides, to be followed later by other relapses so characteristic of this fever, which are variable in number and duration.

With the progress of the disease, the liver and spleen become tender and enlarged; there is increasing anemia and progressive loss of weight. Obstinate constipation is the rule, although in severe cases there may be diarrhea. The drenching sweats, usually nocturnal, continue and may be very distressing. Symptoms of neuritis may appear now, with chronic sciatica or intercostal neuralgia as the most frequent manifestations, although practically any nerve may be affected.* Painful hyperesthesia of the feet, which is aggravated by pressure of the bed clothes, is not uncommon. An acute, transient arthritis, involving one or more joints, often occurs, the affected joint being hot, swollen and extremely tender, the process rapidly subsiding in a few days in one joint only to recur in others. Involvement of the sacroiliac joints is especially painful. An acute orchitis is not infrequent. With the repeated relapses, the patient becomes more and more emaciated, anemic, debilitated and despondent. He is subject to attacks of bronchitis or even at times to bronchopneumonia. The pulse rate becomes increased, and cardiac palpitation occurs on slight exertion. Rheumatic or neuralgic pains are

*For discussion of neurological aspects of brucellosis and extensive bibliography, see Roger, Henri (1932): *La neuromélicococcie*, Presse Medicale, 40: pp. 735-738.

common. The temperature now tends to become intermittent, and this feature, with the cough, emaciation and profuse night sweats, is very suggestive of phthisis. Toward the end of the third month the temperature becomes normal in the morning with only a slight evening pyrexia. This is followed by a period of subnormal temperature and improvement in all symptoms, and convalescence is now established. Complete recovery is slow, however, and for a number of months he is liable to attacks of neuralgic pains, arthritis or orchitis with the return of slight pyrexia. The duration of pyrexia in the average case is about 60 days, the usual length of each pyrexial wave being about 10 days. The period of invalidism from the disease averages three or four months but may persist for two or more years.

4. **Intermittent Form**—The onset is more gradual, the general course of the disease is milder than in the undulatory type, and relapses are less frequent. At the onset, there is a sense of weakness and lassitude with slight evening headache. The appetite is diminished, the tongue is coated, and the individual notices a bad taste in the mouth on waking in the morning. The temperature is normal or subnormal in the morning, rises to about 99° F. in the afternoon and returns to normal during the night. The headache becomes more noticeable, general muscular pains occur, and there is restlessness, insomnia and nocturnal sweating. Constipation is a noticeable feature. The pyrexial curve now assumes its characteristic form. The temperature is normal or nearly so in the morning, rises slowly to a maximum of 99°-105° F. between 2-5 P. M., often associated with chilliness, and falls gradually to normal during the night, the pyrexial fall being accompanied by profuse sweating. This hectic type of temperature may persist for days without serious complications, and, except during the afternoon when the fever is high, the patient eats well and has few complaints.

Fleeting joint pains, neuritis and orchitis may occur in the later stages of the illness. The pyrexial period seldom is prolonged beyond six weeks, but the disease may persist for six months or more. Hardy and also Simpson and Frazier consider the intermittent type to be the most common one in infections with *Br. abortus* in the United States. In the experience of these observers, the average duration of the disease is three or four months.

5. **Malignant Form**—This type, as described by Hughes, is responsible for most of the deaths in undulant fever, but fortunately is rare. The onset usually is sudden with severe headache, pains throughout the body and marked gastric symptoms. The temperature on admission may be 104°-105° F. Abdominal tenderness is present, and the breath and skin odors are very offensive. After several days of continuously high temperature, pulmonary congestion and bronchopneumonia may appear. Diarrhea with frequent and very offensive stools may be present. The temperature may decline slightly but usually remains around 103° F. Cardiac irregularity, increasing pulmonary congestion and obstinate vomiting occur, followed by delirium which soon passes into coma. The patient becomes incontinent, the temperature rises steadily, the heart fails, and the patient dies from hyperpyrexia and toxemia. In 45 fatal cases cited by Hughes, 27, or 60 per cent, died within the first month of the disease.

Both the clinical and the laboratory diagnosis as well as an adequate understanding of the nature of brucellosis can be aided by a study of the pathology of the disease. It is essential to know what tissues are affected when one attempts to isolate the causative microbe. However, there is nothing pathognomonic about either the gross- or the histo-pathology of any of the brucella infections—the pathology is not specific. However, there is a tendency toward involvement of the lymphatic tissues, especially the spleen, and the pregnant uterus and the testicles especially of cattle. The joints are frequently involved, as is also the bone and marrow, (101) the subcutaneous tissues as in fistulous withers of the horse, (102), (103) and rarely (or perhaps more frequently than is supposed) the central nervous system. The udder is a common seat of microscopic lesions in the cow and goat.

The pathology is suggestive of that of tuberculosis, partaking of a chronic inflammatory character. There are foci of infection, often numer-

ous, macroscopically very much like the tubercle and microscopically found to consist of a group of epithelioid cells among which may be found lymphoid cells. Some foci are composed mainly of large cell elements, while in others the cell masses are largely of lymphoid elements. In some foci, plasma and giant cells are seen, and occasionally polymorphonuclear cells. In chronic cases the tissue changes show signs of organization into connective tissue. Abscess formation occurs as does an inflammatory condition of the uterine mucosa.

Huddleson (73) has summarized the descriptions of the pathology of the various forms of brucellosis. The gross changes produced in the organs of the guinea pig were first described simultaneously by Smith and Fabyan (104) and by Schroeder and Cotton (105). The gross changes have been fully described by Henry, Traum and Haring (106). Fabyan (107) has described minutely the histological changes which occur in the tissues of the infected guinea pig.

There have been many descriptions of the affected bovine uterus and fetal membranes. Hallman (108) and associates have made an intensive study of this phase of the pathology of brucellosis. Smith (109) and also Hallman and associates have studied the *Brucella* pneumonia of the bovine fetus.

An aspect of animal brucellosis peculiarly important to human health is udder infection. Cooledge (110) and Tweed (111) have studied the cellular and agglutinin content of affected milk. Runnells and Huddleson (112) and also Sholl and Torrey (113) have described the pathology of *Brucella* mammitis of the cow. The pathology of *Br. suis* infection in a sow is described by Smith (114) and by Johnson and Sholl (115).

Hughes (1) (pages 150, 156 and 175-176) gave a few sketches of the pathology of human *brucella* infection. They are quoted directly:

In very mild cases sexual desire may be increased, the sexual organs partaking in the generally increased nervous susceptibility. Menstruation only disappears in severe cases, and in those in which anaemia is marked. Attacks of this fever have not caused abortion in pregnant women, in the few instances which have occurred in the practice of the writer.

Attacks of this fever, especially when combined with epididymitis, have been accused of causing sterility. This has not been proved by any facts, while the Maltese are a most prolific race. It is certainly not the case with females. The writer has met with an instance in which a wife became impregnated a month after recovery from a mild attack of this fever (40 days' pyrexia) when her husband was in the middle of a severe and prolonged attack of the same disease, but during a temporary apyrexial period. The pregnancy went on successfully to term.

Epididymitis and orchitis (usually single), occur in about 4 to 5 per cent of cases, and are late symptoms. Such conditions are met with more commonly during relapses after apparent convalescence has been established, and may be acute or subacute in character. Suppuration is most uncommon, but occurred in one of the writer's cases, accompanied by a superficial abscess over the ensiform cartilage, both being apparently accidental and due to causes other than the fever virus.

When acute in nature, the testicle and epididymis swell, in from 24 to 48 hours, to the size of a small orange, are very painful and extremely tender. There may be some redness of the skin and effusion into the tunica vaginalis. The condition has no connection with antecedent attacks of gonorrhea, and very many men who have suffered from gonorrhea previously, go through an attack of Mediterranean fever without any testicular trouble. The acute inflammation usually subsides in the course of a few days, leaving the organ hard and slightly tender. Gradually the hardness disappears and the normal condition is returned to, but this often takes a considerable time. The subacute variety is merely a less acute form of the above, the patient complaining of pain and a feeling of weight about the testicle,

especially after exertion or exercise. On examination the epididymis is found to be enlarged, and the whole organ somewhat tender when squeezed even gently. A few days' rest and support relieves the distress, though it may return if exercise is taken before it has quite recovered.

* * * * *

Though slight swelling of the joints may very occasionally occur in enteric fever, it is a common symptom in undulant fever, more especially in the later stages of the disease, passing from one joint to another, but especially affecting the extremities, combined with effusion and occasional redness. Troublesome rheumatic and neuralgic symptoms are very common complications and sequelae of undulant fever, while orchitis and mastitis may occur.

In undulant fever during life, and more especially during post-mortem examination, the writer has observed in severe cases a characteristic goat-like odour not present in enteric fever, but comparable to those present in typhus and rheumatic fevers. During life this is noticeable about the skin and breath.

* * * * *

Dr. Hewlett embedded the specimens in paraffin in the ordinary manner, cut sections with a rocking microtome and stained them with Ehrlich's haematoxylin and eosin. (Hughes)

They show the following appearances:—

Heart—The small vegetation on the mitral nerve has become nearly fully organized into fibrous tissue, and though it is still infiltrated with round cells undergoing change, it cannot be of very recent origin.

Lung—The perivascular and interalveolar tissue is infiltrated with round cells (leucocytes). The air vesicles contain large catarrhal cells and shreds of fibrin, indicative of catarrhal pneumonia.

Liver—Neither fatty or fibroid changes are present. There is cloudy swelling of the liver cells, which have stained badly and show granular degeneration of their protoplasm.

Spleen—Beyond a larger proportion than usual of lymphoid tissue there is apparently nothing abnormal.

Peyer's Patch—The epithelium is continuous over the surface of the gland. There is slight infiltration and increase in the lymphoid cells. Otherwise the section of the intestine through a Peyer's patch appears to be normal.

Kidneys—There is cloudy swelling, granular degeneration and loss of nuclei in the lining epithelium of the tubules, pointing to tubular nephritis. In places there is infiltration of round cells into the intertubular connective tissue, with commencing interstitial change. The glomeruli are normal.

These appearances are not in any way specially characteristic of undulant fever, but are rather those of severe and prolonged pyrexia, acting on the tissues of the body.

Professor A. E. Wright, of Netley, has also cut sections of the spleen, liver, kidney, and brain, of Case No. 14 for the author. These showed the same signs of continued tissue irritation, much marked in this case in the brain, and in and around the tubules of the kidney.

Hardy et al. (31) described the gross and histopathology of some human cases. Hansmann and Schenken (116) gave a complete description of a fatal human case of meningo-encephalitis due to *Brucella*.

Recently, in "Health News" (N. Y. State Dept. of Health Vol. IX, No. 36, Sept. 5, 1932) it was reported:

"Patients with undulant fever not infrequently complain of abdominal pain. Reports indicate that in certain instances the symptomatology tends to simulate that of appendicitis. Possibly the inflammatory reaction in some cases of appendicitis may be due to *B. abortus* infections. A study of

blood specimens (about 10 c. c.) from patients with abdominal pain would thus be most important."

It is not pertinent to our purpose to go further into the special clinical features and complications of the disease, interesting and important as they are to the medical practitioner. The appearance of the patient; the character of the fever, the peculiar skin reactions; the peculiarities of the disturbance of the respiratory, digestive, lymphatic, cardiovascular and nervous systems; the blood picture; and the changes in the special sense organs, joints, bones, muscles and especially the genito-urinary system are all matters outside the scope of this study.

Differential diagnosis has no special interest in this study. It will suffice only to enumerate some of the diseases for which brucellosis may be mistaken, for in the words of Bassett-Smith (1922) (117) "nearly every case of undulant fever has in its early stages been treated for malaria or some pyogenic disease before the correct diagnosis has been made".

Gentry (100) calls attention to the following diseases that may be involved in the differential diagnosis of brucellosis: typhoid and paratyphoid fevers, tularemia, tuberculosis, malaria, rheumatic fever, subacute bacterial endocarditis, pyogenic septicemia, visceral leishmaniasis, tertiary syphilis, and Hodgkin's disease. Cases have been diagnosed as influenza or "flu" by the physician in charge and as brucellosis by the laboratory.

Of special interest to the epidemiologist and to the practitioner is the occurrence of *Brucella* infection in children. In a paper, "Undulant fever (*Brucella* Infection) in children," Dr. John F. Sander (118) reviewed the literature on this subject and reported on six cases. He stated his belief that the infection is much more common in children than is suspected and that many of these cases in children are being diagnosed as influenza or intestinal "flu", summer complaint, rheumatic fever, malaria, tuberculosis, adenoid or tonsil infection, gastro-enteritis, worms, teething, and "what-not".

Serological—Agglutination Test, Complement Fixation Test

Wright (1897) (119) first demonstrated the value of the agglutination test in the diagnosis of undulant fever of man. Zammit (1906) (20) used it effectively to determine that many of the goats of Malta were infected with or carriers of the so-called micrococcus of undulant fever. The technic of the agglutination test will be presented in greater detail when the "Eradication or control of sources of human infection" is discussed. There is no reason to believe that the technic employed in animal disease control is not applicable to the blood of human patients. Certainly far more study has been given the development of a satisfactory procedure by the veterinary serologist than by the student of human serological problems. It is interesting to note at this time that Huddleson (1930) (34) found his rapid or plate method, when used at the bedside superior to the test-tube method employed in the Civil Central Hospital of Malta.

In the interpretation of the agglutination test, it is well to keep in mind that the absence of a reaction does not always justify the rejection of a diagnosis of brucellosis.

Carpenter (1926) (120) and others have shown that positive blood cultures may be obtained from patients who give negative agglutination tests. The reaction may be slow, incomplete, and in low dilutions only. Non-specific reactions and zone phenomena are observed and are best

avoided by employing only standard antigen and technic. Any difficulties with so-called paramelitensis and para-abortus sera must be met by the use of suitable antigens for the test.

Carpenter et al. (1929) (121) examined 4,050 Wassermann blood samples at Syracuse, N. Y., and found 7.3 per cent to contain abortus agglutinins. *Br. abortus* antigen was agglutinated by 2.4 per cent of 955 similar samples collected in New York City. They came to the conclusion that agglutinins in milk (pasteurized) could not affect the agglutinin titer of one who consumed such milk, but that *Br. abortus* agglutinins in the blood are due only to the active stimulation of the body by the living organisms. *Brucella* agglutinins were found to persist in high titer in one case two years after apparent recovery from the disease.

McDaniels (1932) (122) found in an epidemiological study of Illinois cases that "non-specific agglutination reactions with the sera of certain febrile patients can possibly be ascribed to re-stimulation and reliberation of latent antibodies formed during a real infection with *Brucella* organisms some time earlier in the patient's life."

It is not possible to state definitely what constitutes a reaction to the agglutination test in terms of dilution of the serum or in terms of the amount of serum used. It is necessary to know the sensitivity of the antigen employed which indicates the desirability of adopting a standard procedure for making antigen and also for using it.

The complement fixation test does not agree perfectly with the agglutination test with respect to results, but the agreement is so close that in practice the simpler agglutination test may be employed to the total exclusion of the very complicated complement fixation test.

Sasano et al. (1931) (123) report that the examination of sera from 1,000 persons revealed a positive complement fixation for *B. abortus* in 96 and a positive agglutination in 78. In only five cases was the diagnosis of undulant fever made. In each of these five cases complement fixation was positive, and agglutination was present in titers of from 1:135 to 1:1,200 at some time during the illness. Experiments on rabbits show that the complement-fixing substances and the agglutinins develop at about the same time, and that the complement-fixing substances persist longer than the agglutinins. Complement fixation and agglutination may be obtained for months to years after apparent recovery from the infection. Because of this the diagnosis of undulant fever should not be made on the basis of a positive complement fixation or on that of sera producing an agglutination in dilutions of 1:15 or 1:45 in the absence of a positive blood culture.

Gilbert and Coleman (1931) (124) described a simple presumptive test for agglutination. Preliminary results showed that the test permitted examination for evidence of undulant fever, of large numbers of specimens received for other types of examinations. 81,848 sera submitted for complement-fixation test for syphilis were tested by this procedure; 369 when reexamined by the routine method reacted in a 1:80 or higher dilution. In 44 instances undulant fever was indicated. These findings were in sharp contrast to the results on 1,186 sera submitted for agglutination test with *B. typhosus*, 70 of which gave reactions at 1:80 or higher dilution, and 57 of the total were from patients having symptoms of undulant fever. Of 1,255 specimens accompanied by a request for test with *Br. abortus*, 145 gave reactions and 102 of the total were from probable cases of undulant fever. The relatively large number of instances in which a diagnosis of

undulant fever has been made by these tests not only justified them, but indicated that the syndrome of infection with organisms of the *abortus-melitensis* group is still frequently unrecognized.

Rether (1929) (125) described a technic for the precipitation test and experiments with its use. He concluded that extracts of organs and of abomasal contents of aborted fetus and extracts of infected afterbirth do not contain a precipitinogen sensitive to specific sera of high titer. Such extracts were unsuited for diagnosis. With cultural extracts more favorable results were obtained and in many cases such extracts demonstrated specific precipitins, but due to the high per cent of error this reaction was not adaptable for diagnostic purposes. There is no reason to believe that a precipitation test has been developed for the diagnosis of human brucellosis.

Allergic Skin Tests have been studied since Fleischner and Meyer (1918, 1919) (126) demonstrated that a positive intradermal test was a reliable index of infection in guinea pigs. They used both *Br. abortus* and *Br. melitensis* as infecting organisms. Stafseth (1920) (127) came to the same conclusion. He found that guinea pigs injected with dead *Br. abortus* did not react to the intradermal test. He employed a physiological salt suspension of the dead bacteria such as had been used by Reichel and Harkins (1917) (128). The reaction consisted of an area of induration varying in size from 0.5 cm. to 1.5 cm. in diameter and appeared about 24 hours after the injection. An area of decided redness over the swelling was noted in guinea pigs with light skin. An area of necrosis appeared in the center of the swelling after two or three days.

Burnet (1922) (129) injected 0.1 to 0.5 cc. of broth culture filtrates of killed *Br. melitensis* (melitine) (abortine) intradermally in cases of undulant fever negative to the agglutination test with positive results. A local reaction with edema and reddening appeared in about six hours and lasted for several days. Mitra (1924) (130) and Bua (1926) (131) used killed cultures suspended in salt solution. Giordano (1929) (132) also preferred heat-killed salt solution suspensions of *Br. abortus* to culture filtrates. But Huddleson (1930) (34) found that the dead bacillary bodies caused too great a local reaction involving considerable necrosis. He used a filtrate of cultures of all three species,—*Br. melitensis*, *Br. abortus* and *Br. suis*—after prolonging the cultivation for a considerable time. The test was made by injecting about 0.05 cc. of the filtrate intracutaneously on the internal face of the upper part of the fore-arm. The reaction might appear at the sixth hour after injection and persist until the fortieth hour. It was characterized by a circumscribed edema four to six centimeters in diameter, by erythema and pain about the point of injection. If there was no edema, the reaction was considered negative. The reaction was especially valuable in cases negative to the agglutination test. Some cases of the disease gave a negative reaction to the intradermal test. Some individuals who have had the disease and those who have become sensitized to the germ through working with it in the laboratory or by handling infective material showed a typical reaction.

There is another type of reaction which has been studied by Huddleson and Johnson (1930) (133). In certain individuals, there appeared a circumscribed edema about three centimeters in diameter in about 20 to 30 minutes after injection; then the edema extended to a diameter of about six centimeters. The erythema appeared at first about the swelling, then enlarged and covered the surface of the area. The reaction might disappear

in about ten hours or persist for forty hours. There was also a serious general reaction, the symptoms of which were the classical symptoms of undulant fever. Those who gave this type of reaction were especially sensitive to the germ, but this reaction was not one of infection, but it might occur in immunity. The skin reaction was called "*Brucella erythema*".

However, according to Jadassohn (1932) (134) the immediate urticarial reaction appearing in veterinarians after obstetrical maneuvers on cattle, and attributed by Huddleson and Johnson to contact with material infected with *Bang bacillus*, was due to normal bovine substances present in the bouillon culture filtrate employed; it did not appear after tests with *Bang bacillus* in physiological saline, but did after bovine bouillon and allantois fluid. The twenty-four hour papulous eruption, however, was undoubtedly due to *Bang bacillus* for it appeared after the first test, but not after the other two.

Opsonocytophagic Test

Recently Huddleson and Johnson (1931) (135) have reported on the phagocytic activity of the polymorphonuclear cells in the blood of man toward *Brucella*. Huddleson has summarized his findings thus: It has been found that the blood of individuals who have never knowingly been in contact with *Brucella* infective materials or who have not had undulant fever, possesses little if any phagocytic activity for the organism when mixed with it *in vitro*. The polymorphonuclear cells of those who have handled infective materials, such as cultures or infective tissues, and of those who have recovered from undulant fever have marked phagocytic activity. From 80 to 100 per cent of these particular cells will ingest *Brucella* to a marked degree.

During the course of the disease in man, the phagocytic activity of the cells will vary. As a rule, only slight, if any, phagocytosis will be seen. As recovery takes place, the phagocytic power of the cells increases rapidly. There appears to be no relationship between the agglutination titer of the serum and the phagocytic activity of the cells in the same individual. Phagocytosis may be negative when the serum shows a titer of 1 to 2,000, or 100 per cent of the cells may show a marked phagocytosis when serum agglutinins cannot be demonstrated in a 1 to 25 or higher dilution.

The phagocytic activity of the polymorphonuclear cells in individuals who have recovered from undulant fever appears to persist for a considerable length of time. These cells of one individual three years after recovery show a phagocytosis of 100 per cent.

Cultural Methods

The most reliable means of diagnosis of brucellosis would be the isolation of one of the species of *Brucella* from the suspected individual, but there are insurmountable difficulties which limit the usefulness of this method as a routine procedure.

Blood culture is the most promising and has been practiced in *melitensis* infection since the demonstration of the etiological relationship of the specific microbe to the disease. In his studies in Malta and Tunis, in 1929, Huddleson (1930) (34) attempted to answer these questions: Is it necessary to employ a special medium for the isolation of *Br. melitensis* from the blood of man? Is it possible to obtain a culture of the germ with the same degree of success during the course of the disease as during its initial

stages? Is the apyretic period which lasts for many days between febrile attacks as favorable a time for culture as is the pyrexial period? Does it make any difference whether the culture is made during the forenoon when the temperature is normal or in the afternoon when there is an elevation of temperature? The answers to these questions are found in the report of the bacteriologist (1930) (136). The isolation of *Brucella melitensis* from human blood can be accomplished with much more ease and with a higher degree of success if a special medium such as beef or veal liver infusion bouillon (Stafseth, 1920) (72) be used for the purpose. The time interval between inoculations and initial growth of *Brucella melitensis* from blood is, on the average, about 72 hours, but, occasionally, 15 days of incubation are required for initial growth to occur. The pyretic period is the most favorable time for obtaining the organism in culture from the blood. Delay in the inoculations of the medium after procuring the blood specimen postpones the initial growth of *Br. melitensis*. Urine culture is attended with less success. Repeated attempts may be necessary before cultures are obtained as was shown by Kennedy (1905-7) (137). Stool culture has little diagnostic value. However, Amoss and Poston (1929) (138) have successfully isolated *Brucella* by using a method of concentration by agglutination with specific serum before plating cultures. Splenic puncture for the purpose of securing inoculum for culture is hardly warranted. In lactating women, milk may yield cultures. Any local lesion such as abscess or infected joint may be a source of inoculation for cultures.

Successful culture will depend upon the proper procedure, with respect to the provision of aerobic conditions or an atmosphere of CO₂, the use of liver media, a pH of 6.6 and perhaps the use of bacteriostatic dyes. Guinea pig inoculation may be resorted to when *in vitro* cultural methods fail. Differentiation of the species should be attempted according to the methods suggested by Huddleson.

Summary of Laboratory Diagnosis

In a study of the opsono-cytophagic power of the blood and allergic skin reaction in *Brucella* infection and immunity in man, Huddleson, Johnson, and Hamann (1932)* reported that they had found that there was an important relationship between the state of susceptibility to infection with *Brucella* in humans and the ability of the polymorphonuclear cells in whole citrated blood to ingest either *Brucella melitensis*, *Brucella abortus* or *Brucella suis* *in vitro*. The phagocytic activity of the polymorphonuclear cells was correlated with the intradermal test in differentiating between the susceptible, the immune, and the infected. The intradermal test was made with a nucleo-protein isolated from the organism. Those susceptible to infection with *Brucella* showed no intradermal reaction and the cells showed little if any phagocytosis. Those that have acquired an immunity to *Brucella* infection gave a positive intradermal reaction and the cells showed a marked phagocytic activity. Those that were infected gave a positive intradermal reaction and the cells might show no phagocytosis or varying degrees of phagocytosis. In the infected, the activity of the cells depended upon the state of the disease. When recovery from *Brucella* infection occurred, the polymorphonuclear cells showed marked phagocytic activity. This state of activity of the cells appeared to last for several years. The polymorphonuclear cells in whole defibrinated blood of most humans, cat-

*Read before Ann. meeting of A. P. H. A., Oct., 1932.

tle and a small percentage of guinea pigs showed marked phagocytic activity for *Brucella in vitro*. Normal phagocytosis was prevented by the addition of sodium citrate to a final concentration of 0.8 per cent. This amount of citrate did not appear to interfere with the phagocytic activity of the blood from those that had acquired immunity to *Brucella*. It was possible to prevent phagocytosis by increasing the concentration of sodium citrate in the blood from immunes above the amount just mentioned. There was no relation between the opsono-cytophagic activity of citrated whole blood and serum agglutination titer for *Brucella*.

The studies which they have conducted on citrated blood of humans who were known to have had undulant fever in past years and shortly after recovery, who are actively infected, or who have no history of the disease, showed that the *in vitro* activity of the polymorphonuclear cells in whole citrate blood for *Brucella* was an expression of immunity to *Brucella* and an indication of the progress toward recovery in active infection. The absence of or a low phagocytic activity obtained in conjunction with a negative allergic skin test was evidence of susceptibility to *Brucella* infection.

The following Tables are subject to emendation as further research progresses, but they should be helpful as a guide in diagnosis of brucellosis:

A proposed system for the diagnosis of Undulant Fever according to results of the agglutination, Allergic and Opsono-cytophagic tests.*

Agglutination Test	Allergic Skin Test	Opsono-cytophagic Power	Status toward <i>Brucella</i>
Negative.....	Negative.....	Negative.....	Susceptible
Negative.....	Positive.....	Negative or Slight.....	Infected
Negative.....	Positive.....	Marked.....	Immune
Positive.....	Positive.....	Marked.....	Immune
Positive.....	Positive.....	Negative or Slight.....	Infected

*A study of the Opsono-Cytophagic power of the blood and allergic skin reaction in *Brucella* infection and immunity in man—Huddleson, I. F., H. W. Johnson and E. E. Hamann. Read before Am. Pub. Health Assn., Oct. 1932.

Susceptibility, immunity and infection in Brucellosis indicated by differential laboratory tests.

State	Culture Findings	Serological Tests	Intradermal Test with Brucellin	Opsono-cytophagic Activity of Citrated Whole Blood
Infection.....	+	+	+	— or Sl.
Infection.....	+	—	+	— or Sl.
Infection.....	—	+	+	— or Sl.
Infection.....	—	—	+	— or Sl.
Susceptibility.....	—	—	—	—
Immunity.....	—	+	+	+
Immunity.....	—	—	+	+

Treatment—Curative treatment of brucellosis by the use of drugs or chemicals has signally failed. Hughes (1897, p. 215) (1) gave a good account of this subject covering developments up to the date of his publication. Almost without exception, he found each drug either harmful or not beneficial. He called attention to the unsuccessful use of the following: quinine, bismuth, arsenic, hydrocyanic acid, carbolic acid, boracic acid, chlorine, salol, aconite, colchicum, eucalyptus, turpentine, salicylic acid, antipyrin, antifebrin, phenacetin, and resorcin.

More recently, Hardy et al. (1931) (9) have briefly summarized the status of modern chemotherapy in brucellosis: "In three cases of *Brucella* infection Awe and Palmer report recovery following the injection of non-specific protein. Simpson, however, has found this to be of no appreciable value. Mercurochrome has its advocates, though Ross and Martin consider that in *Br. melitensis* var. *melitensis* infection its value has not been demonstrated. Acriflavine, trypaflavine, colloidal metals, and neoarsphenamine have all been recommended, but the very length of the list shows clearly that the value of any drug, thus far advocated, has not been satisfactorily demonstrated".

Graham and Thorp (1930) (139) found that acriflavine, trypacrin "A", tryparsamide, and colloidal carbon administered intravenously and an iodine preparation called alkali hypiodite given intramuscularly to infected cows did not alter the blood agglutination titer. Probably, the same results would occur in man.

Huddleson (1930, p. 411) (34) had tested the therapeutic value of solution of mercuraphene in cooperation with Dr. R. M. Olin of the Michigan State College Hospital with encouraging results. Its use in Tunis was not attended by success.

Leavell et al. (1930) (140) stimulated by Huddleson's studies on the bacteriostatic dyes *in vitro*, achieved some degree of success in cases of intestinal brucellosis with the use of thionin and methyl violet.

James and Graham (1931) (141) have reported on the use of colloidal carbon with adsorbed flavines and also metaphen on cattle afflicted with Bang's disease. No ill effects were noted and no curative effect was indicated. It is probable that the same results would ensue in man.

Huddleson (1931) (135a) tested iodine compounds, prodin C and M, worked out by Mr. H. E. Brown of Jersey City, N. J. Ten cows that showed agglutinins in the blood and some of which showed *Brucella abortus* in the udder were treated without any influence on the agglutinin titer of the blood or the infection of the udder.

Huddleson suggests in this same report (p. 29) that the growth inhibiting power of thionin and pyronin, especially the latter, offers possibilities in the therapeutics of brucellosis of both man and the lower animals. However, further use of pyronin has not given encouragement (144).

Zeller (1931) (142) stated that among chemotherapeutic agents, trypaflavin, collargol, mercurochrome, and others have been used in isolated cases with alleged success. But, as he wisely observed, often rest in bed and good care alone are enough to cure in a short or little longer time Bang disease in man without special treatment. Therefore, it is difficult to form a reliable judgment if, and how much, (a) the symptomatic fever treatment (salicylic acid, quinine, camphor-pyramidon) (b) the unspecific treatment (omnadin), (c) the serum-therapy (melitensis or Bang immunoserum, convalescent serum), (d) the vaccine therapy (thermically or

chemically killed or weakened brucella-vaccines, heterogeneous vaccines, autolysates), (e) or the chemotherapy (neosalvarsan, trypaflavin, argochrome, mercurochrome, electrocollargol, solganal, methyl violet, thionin, and other preparations that have been used so far) have displayed a favorable effect or not. More experience is necessary here. Further symptomatic experiments with chemotherapeutic preparations seem to be desirable. Concerning vaccine therapy, which is generally not unfavorably criticized, it is to be said that it should be used in hospitals only, at first, because its use has sometimes caused violent reactions in the patient.

Six chemical agents, thionine, neoarsphenamine, acriflavine, sodium cacodylate, pyridium, and butyl chloride, were tested by the Experiment Station of the Federal Bureau of Animal Industry to see if their administration would overcome udder infection in cattle. The results were in all cases negative. (p. 30) (143)

The *melitine* of Burnet (129) and various modifications of it have been employed in the treatment of human brucellosis.

Huddleson (144) has prepared a brucellin which has been used successfully on children (see Sander p. 57) and on over a hundred adults in co-operation with the Battle Creek Sanitarium, Henry Ford Hospital, University Hospital of Michigan, Iowa State Board of Health, the Civil Hospital of Valletta (Malta), and a number of private practitioners. This material is unquestionably of value in bringing about recovery in many cases of undulant fever. The accumulating data indicate that it is of little value in the glandular type.

Johnson (129) (145) studied the bacteriolytic power of serum of human, bovine, equine and caprine sources. Hyperimmune bovine sera and immune human sera seem to have a slightly varying bactericidal zone in dilutions between 1 to 500 and 1 to 64,000. A study of five sera on 235 guinea pigs indicates that the bovine sera have a therapeutic value in dilutions between 1 to 32,000 and 1 to 1,024,000. It is clear that the agglutinin titer is not a measure of the serum's lytic power. It is also apparent that the concentration of the lytic substance in the serum is not in direct relation to its therapeutic power.

Under Huddleson's direction, (1931) (135a) the development of a therapeutic serum for brucellosis has been continued. The antigenic substance used in the preparation of the anti-serum is a culture-filtrate. The animal found most satisfactory for its production is the horse. The new serum possesses a two-fold property,—(a) neutralization of a toxic substances produced by *Brucella* and (b) increasing the phagocytic activity of the polymorphonuclear leucocytes. The serum is extraordinarily labile. Passage through a candle filter or treatment with antiseptics destroys much of its potency.

Preventive Treatment—Dubois and Sollier (1930) vaccinated their laboratory staff, employees of farms where undulant fever was prevalent, and a number of veterinarians, the vaccine consisting of a mixture of three races of *Alcaligenes melitensis* (human, bovine, and caprine), together with a strain of *A. abortus*. The vaccine was heated to 70° C., contained 2,000 million organisms per cc., and was inoculated subcutaneously in two doses of 0.5 and 10 cc. respectively, with a 10 day interval. Local reaction was slight and general reaction absent. All who appear in good health may be inoculated; immunity lasted for six months to two years. When subcutaneous inoculation was contraindicated, vaccination by the digestive tract

was tried. Where animal infections with *A. melitensis* exist, preventive inoculation would seem to be the only means of protecting man from infection and should be practiced on all whose occupations bring them into contact with animals susceptible to infection, according to these authors.

Of the various methods tried for producing melitensis antigens, in an effort to reduce their toxicity for mice and rats, Fischera and Maugeri (1930) (147) found that treatment with the following reagents gave products of decreasing toxicity: (1) for rats—formol, fluid chloroform, phenol, iodine, heat, ether, chloroform vapor and yatren; (2) for mice—formol, fluid chloroform, phenol, H_2O_2 , heat, and iodine had similar toxicities, also NaF, ether, chloroform vapor and yatren, the last being $\frac{1}{8}$ as toxic as formol.

Van der Hoeden (1932) (148) found that the administration of a killed *Brucella* culture by mouth did not result in the formation of agglutinins or amboceptors in the horse. The oral administration of living *Brucella* culture quickly produced agglutinins and complement fixing antibodies. The subcutaneous injection of a killed *Brucella* suspension was found to set up an allergic reaction in horses affected with brucellosis, including a fever of two days' duration, swelling, and as a rule, abscess formation at the place of injection. The ophthalmic test with a preparation of *Brucella* was negative in 23 noninfected horses and clearly positive in the seven horses affected with brucellosis.

The effects of vaccination of cattle by means of single or repeated injection of a live culture avirulent (for cattle and guinea pigs) vaccine has been studied. The culture, *Br. abortus*, and its use in the vaccination of cattle will be discussed under the caption: "Eradication or control of sources of human infection—*Brucella abortus*—vaccination." It will suffice at this place to call attention to the possibility of the use of this culture in the vaccination of humans who are exposed to unusual hazards of *Brucella* infection, whether it be from *abortus*, *suis* or *melitensis*. Accidental inoculation of this culture into the skin of a worker has occurred in our laboratory and a moderate local and a general febrile reaction was experienced. The possible efficacy of a devitalized vaccine or bacterin is doubtful. There has not been developed a satisfactory method of divitalizing the microbe without denaturizing the bacterial protein, the antigenic substance.

There are circumstances under which an effective immunizing agent that can be safely and economically administered to man should be available. In Malta and in countries of the Mediterranean littoral, where brucellosis of goats is prevalent, it is not so easy to protect the native population by means that are effective in the United States because of the antiquity and fixity of the practices and *mores* of the people and their consequent unwillingness to adopt new methods or to put themselves to present inconvenience in order to avoid later disaster. Laboratory workers, veterinarians in cattle and swine practice, livestock men, and packing house employees in countries where brucellosis is a problem might profit by a safe and efficacious immunizing agent. None is available to our knowledge, but the avirulent live culture vaccine of Huddleson is worthy of trial.

Without doubt, the most logical procedure in the control of human brucellosis is to attack it at its sources, to dry up the reservoirs of infection. As has been seen, these are probably all of animal origin. The problem is one of animal disease control, the proper surveillance of dairy food

products and meat food products, of special precautions on the part of the laboratorian, the veterinarian, the butcher, and the animal husbandman.

McCoy (1931) (149) says of the problem:

"We now know it (undulant fever) is tolerably prevalent in the United States, although a few years ago we knew nothing of it save that occasionally some one was infected from goats in the southwestern part of the United States. We now know that people often are infected by handling diseased swine or cattle. Sausage makers seem to be especially liable to the disease from handling the carcasses of hogs. One of the most controversial points in respect to this disease is as to just how far the infection is due to cow's milk.

"The evidence now available suggests that perhaps half the cases we have in this country are derived from milk. The prevention of *milk-borne undulant fever* is quite simple: Use only pasteurized or boiled milk and there will be no danger. That this really works in practice is evident by the fact that in communities in which all milk is pasteurized the disease is unknown, while individual cases and small outbreaks occur when milk is not pasteurized. Of course, there are other good reasons for the pasteurization of milk; the risk of undulant fever is to be looked upon as an additional reason.

"The prevention of the cases not due to milk, those due to contact with infected animals or animal products, is unsatisfactory. It is encouraging, however, to know that veterinarians are steadily going forward in research in this important field and that we may look hopefully to the time when the disease in animals can be either abolished or brought under very definite control—and therefore the source of human infections will be eliminated."

Is undulant fever an industrial hazard and compensable under the workmen's compensation act?

This question may require an answer in the case of *Brucella suis* infection acquired by butchers in hog packing plants.* An abattoir case con-

*The following Court Decision on Public Health indicates that it is not clone slaughter house cases that may be the basis of an action for damages.

Undulant fever held compensable under workmen's compensation act.—(Idaho Supreme Court; *CROWLEY v. Idaho Industrial School et al.*, 26 P. (2d) 180; decided Oct. 19, 1933.) An employee of the Idaho Industrial Training School, who was classified as an instructor of dairying, was required by his duties to care for a herd of dairy cows at calving time and after the calves were born, to treat the cows with disinfectants by inserting his hand and arm into the bodies of the animals. Some of the cows in the herd were infected with contagious abortion. The employee contracted undulant fever and sought compensation therefor under the workmen's compensation act. The supreme court affirmed a finding by the trial court that the injury for which compensation was claimed was an accident, arising out of and in the course of the employment, stating, in part, as follows:

Appellants' first assignment of error presents the question of law as to whether, under the facts and findings, the alleged injury for which respondent seeks compensation is a compensable accident arising out of and in the course of his employment, or an occupational or industrial disease or sickness not arising out of and in the course of his employment and not compensable. * * * We cannot say from the record before us that there is not sufficient competent evidence to sustain the court's finding that the injury received by respondent resulted from the exposure to the disease by the method necessarily followed in treating the cows. * * * Respondent's treatment of the cows, as found by the court, was an incidental duty among other numerous duties he was required to perform as a dairy instructor. There is evidence that the usual source of undulant fever infection is through the human digestive tract from taking raw fat or milk, and that contracting it by coming in contact with cows carrying the germ is not prevalent nor is it a condition frequently met. The evidence bears out the conclusion that the contracting of undulant fever is not inherent in the handling of cows, nor is it the customary or usual result or concomitant of the occupation and mode of work followed by respondent.

* * * * *

If the injury sustained by respondent was not one inherent to his occupation as commonly understood, but an accident as used in the popular and ordinary sense of the word, as denoting an unexpected or untoward event which is not expected or designed, his recovery cannot be denied upon the theory that the injury resulted from an occupation disease and not from an accident. We are inclined to the view that the proper rule to be applied in the case at bar is announced in the case of *Reinoehl v. Namacher Pole, etc., Co.*, 51 Idaho 359, 6 P. (2d) 860; *Ramsay v. Sullivan Min. Co.*, supra.

Public Health Reports, 49, 1934, pp. 346-347.

tracted from cattle has already come into court with a resultant affirmative decision. (1932, *Ingelfinger v. Dold Packing Co.*) (150):

On November 6, 1930, a young butcher became ill of undulant fever and suffered in consequence from inflammation of his heart's lining membrane. The Department of Labor (New York State) awarded compensation to him for resultant disability. Undulant fever is a germ disease contracted from cattle either through cuts or other body wounds or through milk, butter or cheese taken as food. It causes endocarditis. Evidence in the case was that the butcher had cut the fingers of his hands on three separate occasions in August, September and October, 1930, while skinning the feet of cattle and that he had eaten no food anywhere else than at his sister's home during the period. The carrier contended that no other employee at the plant, and the employee that no other member of the sister's family had contracted the disease. Award unanimously affirmed.

The following case may also serve as a legal precedent for a court decision in brucellosis cases:

In a negligence action brought to recover damages, (*Kentucky Court of Appeals; Great Atlantic and Pacific Tea Co. v. Sexton*, 46 S. W. (2d) 87; decided Feb. 2, 1932) it was alleged that the plaintiff, while an employee of a meat market, contracted tularemia in the course of his work of skinning and dressing rabbits. At the time the plaintiff dressed the rabbits, he had a small abrasion or scratch on one of his fingers. A jury returned a verdict in plaintiff's favor and, from the judgment based thereon, the company operating the meat market appealed. (151)

The court of appeals, in passing on the matter, said that there was a determination the question of whether or not the injury was compensable under the workmen's compensation act. The pertinent portion of such act read as follows:

This act * * * shall affect the liability of the employers subject thereto to their employees for personal injuries sustained by the employee by accident arising out of and in the course of his employment or for death resulting from such accidental injury: Provided, however, that personal injury by accident, as herein defined, shall not include diseases, except where the disease is the natural and direct result of a traumatic injury by accident. * * *

The court, after considering the meaning of the word "accident" reached the conclusion that the injury in the instant case "was sustained by accident" within the meaning of the compensation law, and then turned to the question of whether the disease was the "natural and direct result of traumatic injury" within the meaning of the compensation statute. In this connection there was quoted a definition of "trauma" by Webster as being "a wound or injury directly produced by causes external to the body," and concerning this the court said:

It will be noted that this does not include within its scope and meaning only physical force in the sense of a blow, a current of electricity, or like terms implying power, vigor, violence, or energy in the commonly accepted meaning of its terms, but may be as consistently construed to include any independent influence or cause external to the body coming into direct contact with and causing injury to the physical structure thereof.

It was pointed out that the injury in the present case could be traced directly to the employee's coming in contact with meats laden with tularemia germs; that the time, place, and cause of the injury were determinable with reasonable certainty; that, as an immediate result of the contact, symptoms peculiar to the disease manifested themselves; and that it was not a gradual development arising out of natural dangers incident to the employment but was sudden, unexpected, and unusual, without any of the distinctive features of an occupational disease. The conclusion reached by the court was that the employee's disease was "the natural and direct result of traumatic injury by accident sustained while in the course of his employment".

The judgment of the lower court was reversed and the cause remanded for another trial and proceedings consistent with the opinion.*

Martin and Myers (1931) (152) found, in Nebraska, *Brucella* antibodies in sera from meat packing employees as follows: Fifteen per cent

*Another case is reported in Public Health Reports, 49, 1934, p. 465.

of 100 employees with 18 months on the company's sick list with symptoms suggestive of undulant fever, and three per cent of 100 other employees.

Huddleson (135a, 144) has made a study of swine brucellosis in packing plants and on farms and also in packing houses employees.

There is much evidence that brucellosis is an industrial hazard. Jordan (1931) (153) reported that since nearly 80 per cent of the group of the general population has been shown to have no contact with livestock, it is assumed that their agglutinins for *Brucella* are largely due to use of raw dairy products. Veterinarians showed agglutinins for *Brucella* in definitely higher ratio than did the general population, owing chiefly to contact with cattle, but the titers did not tend to reach high dilutions, ordinarily indicative of active infection, owing possibly to an acquired immunity. Infection with *Br. melitensis* and manifest disease due to contact were in direct proportion to exposure. Infection with *Br. melitensis* and disease due to ingestion of raw dairy products from infected animals seem to be largely dependent on amount consumed, duration of exposure and number of organisms ingested. Immunity probably played a significant role in the epidemiology of undulant fever, if one judges from the large per cent showing "no agglutination" in the various selected groups. Some of those in the "no agglutination" groups came to have the negative reaction following infection associated with disease, a larger number apparently following infection without disease. Others showed no agglutination through freedom from exposure to infection. He asks, are there also other factors, e. g., natural immunity in children or groups of other ages?

Thomsen (1931) (154) reported that up to April, 1931, diagnosis of undulant fever had been made in only six cases among veterinarians in Denmark. All were young men who were taken ill shortly after they had commenced practicing on cattle in abortus-infected stables. That the disease has not been ascertained among older veterinarians is quite in keeping with the fact reported by the author (and later confirmed by others) that nearly all veterinarians (ca. 94 per cent) who had practiced on cattle for more than one year have specific antibodies against *Br. abortus* Bang and are presumably immune. On the basis of the author's examinations, it is warrantable to regard undulant fever as a disease unknown in Denmark prior to 1925. The author suggests that veterinarians be vaccinated, a painful but worthwhile procedure.

Thomsen (1931) (155) describes a peculiar occupational skin lesion, presumably of allergic nature, produced by *Br. abortus* Bang. It appears as an eruption on the arms and, sometimes, on the hands and fingers, consisting in multiple follicular papules, and accompanied by intense itching, pustule formation and necrosis. In severe cases the individual papules become confluent, and the entire arm is infiltrated, red and tender; now the itch is usually very intense, so that the patient is mostly incapable of work. The skin lesion is acute in its onset, developing especially in immediate connection with delivery of the afterbirth in cows with infectious abortion; and it has a tendency to relapse after every subsequent delivery. The eruption may last up to three weeks. In periods when the delivery of placenta is a frequent procedure (in particular the spring) the lesion may be chronic. This skin lesion is rather common, nearly one-third of all the veterinarians graduated since 1915 have had one or several attacks.

According to this author, the eruption may hardly be due to an actual infection of the skin with *Br. abortus* Bang. It is probably an allergic re-

action of the skin to the toxins of this bacillus that are presumably present in considerable amounts in the specific afterbirth exudate, being thoroughly rubbed into the skin of the veterinarian's arm under the delivery of the placenta. The presence of an allergic condition in cases may be demonstrated by a cutaneous test with a preparation produced along the lines of tuberculin preparation. It is called "abortin". Inunction of this preparation into the skin of a sensitive individual produces a reaction that looks exactly like the "spontaneous" eruption, whereas the control individuals, with a very few exceptions, have shown negative reaction. So this eruption is very likely to be interpreted as an allergic reaction; and it seems most reasonable to attribute this allergy to a preceding infection. The skin lesion is not accompanied by fever or any other general symptoms, and it has no resemblance to *febris undulans* Bang. The clinical picture observed by the author differs moreover, in some essential features from several other cases of skin eruptions described in the literature as occurring in veterinary surgeons subsequent to delivery of the afterbirth in infectious cattle abortion. For treatment of this skin lesion, protective remedies are recommended.

Eradication or control of sources of human infection

Brucellosis of man rarely if ever spreads to other humans although it is conceivable that it is contagious from man to man under certain conditions; certainly it is the part of wisdom to take suitable precautions against such a possibility. Fortunately the control or prevention of brucellosis hominis is a problem in animal hygiene or veterinary medicine. The fortunate aspect of the situation resides in the fact that veterinary medicine is better organized for disease control than is human medicine. T. Swann Harding (1932) (156) has sensed the situation accurately and worded it so well that we quote directly:

**** But the real point to be considered is that while human beings are still exposed to really preventable diseases like malaria, tetanus and diphtheria, and while human medical research is sporadic, illcoordinated and frequently involves shameless duplication of effort, so thoroughly has veterinary medicine been organized that the animal is well protected against any pathological condition preventive medicine can eradicate.

(Referring to the recent (1929) effective campaign to wipe out foot and mouth disease in California) **** The method was drastic and sanguinary, but it was effective. The country was protected from one of the most dangerous cattle diseases in existence. The personnel in charge is thoroughly trained, and individuals moved to the focal point as directed from Washington, and performed their duties in a business-like manner. Walking in, killing a man's valuable cattle, paying him the appraised price the government grants, digging a trench with a machine, casting in the bodies, ripping up the hides and covering the entire mess of meat with lime both invades his domain and smacks him squarely in the face with a large gob of state socialism. But it represents organized effort acting effectively in a social emergency and it serves its purpose. In the case of smallpox, however, it is difficult for the authorities to enforce vaccination upon individuals who resent such interference with their "personal liberties". In the case of certain other diseases among humans, eradication would be fairly easy if physicians but conscientiously did their part. Finally, the fundamental tenet of economically organized medicine is individualism, and the slightest tendency towards soundly organized efforts to control disease on a national basis is denounced by the journals of the medical guild as "pauperizing" the public or as state socialism.

It is, of course, very much easier to eradicate animal diseases than to wipe out human ailments because, if you can't do anything else, you can kill a few hundred patients. This does not materially affect the major thesis of the present paper, i. e., that veterinary medicine has been so efficiently organized to combat animal

diseases that the result has been the complete eradication of some diseases and very serious inroads upon the disastrous effects of others; furthermore, that within a very short period of time, the status of the veterinary profession has been raised and effective means have been devised to use without delay the latest findings of an organized body of scientists of various sorts, engaged in fundamental research, in a practical way, to fight diseases among animals.

In short, a sick or indisposed animal is regarded as an acute social problem about which the community, through "socialistic" (if you please) governmental agencies is prepared to take action. But a sick man is not at all sure of such certain expert care—at least not so long as experts insistently inform us that preventable deaths cost billions of dollars annually in America today.*

The ideal solution of the brucellosis problem is the eradication of *Brucella* which could be done by destroying all sources or reservoirs of the various species of *Brucella*. Fortunately these reservoirs are, so far as we know, the domesticated animals, especially the goat, cow, pig, and to a lesser degree, the importance of which cannot now be appraised, the sheep, horse, and barnyard fowl. It is doubtful whether the proved existence of *Brucella* in the dog, water buffalo, elk, and various species of fowl has any practical significance so far as the problem as a whole is concerned. This program of eradication may involve any geographical area or political unit depending upon economic and other circumstances and may be considered a success limited to the section involved except that it must be recognized that the brucellosis-free island thus created may be entirely surrounded by the dangerous water of infection sources. The splendid isolation thus created must be maintained at the price of an eternal vigilance the armaments of which are furnished by modern sanitary science with its scientific understanding of infection and its socially acceptable quarantine and isolation measures. Where more or less complete eradication is not practicable compromise measures must be provided.

Fortunately, especially in this country, there is a varied experience in animal disease control. It will suffice to call attention to the modes of attack that have proved effective against three types of diseases. (a) exotic plagues, (b) a well established geographically limited epizootic and (c) a disease that was probably imported but which is rapidly becoming panzootic. Thus, a decision can be made whether there is a tested procedure which may be followed in fighting brucellosis.

The Eradication of Exotic Plagues—Bovine contagious pleuropneumonia, lung plague, was introduced from the Old World into Brooklyn, New York, in 1843. It spread to states as widely separated as Connecticut to the north, Virginia to the south, and Illinois to the west. It was our good fortune to have in this country a highly trained veterinarian, Dr. James Law, brought to this country from Scotland, to become professor of veterinary science on the first faculty of Cornell University. He was brought over by Andrew D. White, the young president of the newly opened university, on the insistence of its founder, Ezra Cornell. Law (1887, 1912) (157) in 1879 undertook the eradication of lung plague of cattle in New York and New Jersey, but due to lack of public support the results were not entirely successful. The obvious necessity of protecting the cattle trade that centered at the Chicago stockyards made the later effort in 1887 successful. The federal government and the State of Illinois vigorously supported the drastic stamping out methods and in three months the disease

*This article was personally corrected and endorsed by Dr. John R. Mohler, chief of the United States Bureau of Animal Industry in the Department of Agriculture, insofar as it is concerned with the activities of that bureau.

was eliminated from that state. By 1892, the same methods resulted in the final complete eradication of the disease from the United States. As early as 1835, similar attempts were made to stamp out the disease in Holland. After its introduction in 1847 into Sweden, in 1848 into Denmark, and in 1860 into Norway, it was suppressed. As early as 1847 in New Jersey, and 1859 in Massachusetts, outbreaks due to independent importations from the Old World were completely stamped out by slaughter and disinfection.

The pioneer work of suppressing lung plague of cattle in the United States is illuminating in that it was staged at exactly the period when Pasteur and his disciples were laying the firm foundation for a real understanding of microbial phenomena the most conspicuous of which is the phenomenon of communicable disease. It is to the credit of American agriculture and statesmanship that the methods proposed by Law were adopted and supported.

Effective federal quarantine has prevented the reintroduction of bovine pleuropneumonia into the United States and thus this nation has been saved a monetary loss that would have equaled the cost of the Civil War. The disease is not communicable to man or to the other domesticated animals hence the only stimulus to the work of eradication was that involved in the disease as a cattle problem.

Foot and mouth disease furnishes an excellent example of an ever threatening exotic animal plague that has been repeatedly suppressed by the livestock sanitary authorities of the United States. Outbreaks of this epizootic have occurred in this country according to Mohler (1928) (158) in 1870, 1880, 1884, 1902, 1908, 1914, 1924, 1925, and again in 1932. The 1914 outbreak was the most threatening and stubborn. Slaughtering infected and exposed animals promptly, burying or burning the carcasses, disinfection, isolation, and quarantine have been the modes of attack. Compensation to affected owners after liberal appraisalment has made the progress of the work less difficult.

A thoroughly trained veterinary sanitary service in the federal department of agriculture as well as in the involved states has furnished smooth-running machinery for the successive campaigns. A remarkably enlightened and intelligently responsive public has assured the practical success of an otherwise merely beautifully scientifically correct method of attack. This disease will continue to cross our borders in the future but it will be successfully repulsed as in the past. Anything short of prompt and complete suppression of foot and mouth disease in the cloven-footed animals of North America is not to be considered economically permissible. This is a national policy heartily supported by public sentiment. The fact that the disease is communicable to man seems to play only a lesser rôle in the reaction of the public to the disease.

Fowl pest appeared for the first time in the United States in September, 1924. (1925) (159). On December 11, 1924, New York City placed an embargo on shipments of poultry from a number of western states into which this virus disease had spread. On December 17, Congress authorized the use of \$100,000 from the recently created emergency appropriation for foot-and-mouth-disease work. On December 22, B. A. I. Order 291 prohibited the interstate shipment of poultry infected with or exposed to European fowl pest. The eradication work was completed by March 1, 1925. This disease has no direct human health implications.

Lung plague of cattle, foot-and-mouth-disease of cloven-footed animals

and of man, and fowl pest are virus diseases that have left and may again leave their Old World hosts to seek a foothold in the livestock of the northern part of the New World. To combat them, a scientifically sound, socially acceptable, and economically profitable procedure has been evolved. This procedure could not be applied to meet the problems of brucellosis in any country where this disease has become thoroughly established.

Some of the features of the stamping-out method may be adapted to the plans of certain localities or to aspects of a greatly modified general plan far less annihilating in its method. The stamping-out method such as is employed with exotic animal plagues may, or may not, be scientifically sound as a basis for a campaign against brucellosis of domesticated animals in this country. Certainly, it would not be socially acceptable or economically feasible.

A Well Established Geographically Limited Epizootic—Texas fever or bovine piroplasmiasis, was probably introduced into America with the early shipments of Spanish cattle that were to range over what are now the states bordering on the Gulf of Mexico. The peculiar nature of this disease baffled the practitioner and defied the investigator until Smith and Kilborne (1893) (160), working under the direction of D. E. Salmon, Chief of the Bureau of Animal Industry of the U. S. Department of Agriculture, published the classical report on Texas fever, picturing for the first time all the intricate relationships of the *dramatis personae* of a plague tragedy, an insect borne disease. Salmon, Smith, and Kilborne had all been trained by Law who had recently eradicated lung plague.

The elimination of tick fever has been pushed along the lines of tick eradication during a quarter century until Mohler, the Chief of the B. A. I., was able to state in his report of 1931, "The eradication of cattle ticks, which formerly infested 15 Southern States, continued to make substantial gains. With the release of all of Mississippi at the beginning of the fiscal year, the number of States still under quarantine was reduced to four, namely, Arkansas, Florida, Louisiana, and Texas. Notwithstanding many physical obstacles and some scattered opposition, tick eradication is now receiving the support of the great majority of progressive livestock owners and public officials."

The experiences in the eradication of an enzootic, an insect-borne disease limited in its ability to persist to those areas rarely if ever visited by extremely low temperatures especially of long duration, are of little service except in a general way to the campaigner against brucellosis. Tick eradication has furnished some lessons in how to overcome "many physical obstacles and some scattered opposition" and there is reason to believe that the same "progressive livestock owners and public officials" whose support has been built up for the suppression of one menace to animal industry will the more readily support a campaign against another disease equally menacing, more especially since the former cattle disease is not transmissible to man or other livestock while the latter may yet gain the reputation of being zoologically one of the most widespread of diseases. Vaccination against piroplasmiasis has been practiced with some success but tick eradication is the obvious solution.

A Disease That Was Probably Imported But Which is Rapidly Becoming Panzootic Tuberculosis is a disease the origin of which is

buried in antiquity and the distribution of which is universal. It is probably zoologically the most widespread of diseases. It is certainly transmissible from cattle or swine to man. It is not susceptible of curative treatment and there is no acceptable specific preventive treatment and none in prospect unless it be B.C.G. According to Lochead (1928) (161) of Rochester, Minn., it is not likely to be eradicated in any sudden intensive effort by any one method or by all. He thinks it would be foolish to be blind to the many long years of earnest endeavor which will be necessary in the fight, using all methods available and continually searching for new knowledge and new methods. "No good will result in our fight against it by deluding ourselves or trying to fool the public." He realizes, "There are a considerable number of people who do not know or who refuse to learn; and the amount of organized opposition to our efforts to solve the problem indicates that definite propaganda to lower the bars against tuberculosis milk cows continues to be carried on with unabated energy. If the antis are becoming less numerous, they have not lost anything in zeal."

The key to the success of the cattle tuberculosis eradication campaign in the United States is the accuracy of the tuberculin test. It is not absolutely accurate—no biological test is or can be—but it has a high degree of accuracy not surpassed by any other diagnostic test. The method of procedure is called the area plan. The area unit in the states that are cooperating is the county. Kiernan (1920) (162), who had charge of the eradication campaign for a number of years after its inception, gave the uniform methods and rules for tuberculosis-free accredited herds of cattle adopted in 1917 by the U. S. Livestock Sanitary Association, approved by the U. S. Bureau of Animal Industry and accepted by the cooperating States.

Generous governmental financial aid, federal, state and local, has made the adoption of the plan very acceptable to the cattle owner as a rule. The free tuberculin testing of cattle and the liberal appraisalment of and compensation for slaughtered cattle are accepted as proper charges against the public treasury in the name of public health and these measures tend to make the affected cattle owner more cooperative. He, perhaps, is influenced toward a cooperative attitude more because of the ultimate economic advantages accruing from a tuberculosis free herd than because of a deep concern for public health. The writer (1927) (163) in an address before the Lake States Tuberculosis Conference, Lansing, Michigan, June 27, took occasion to point out some of the more discouraging aspects of the problem. The following quotations from that address might be applicable to a similar eradication program directed against brucellosis.

"Our knowledge of tuberculosis is not complete by any means but it has accumulated to such an extent that for a generation there have been those bold enough to advocate a concerted plan of eradication. The speaker asks permission to be numbered in that group. The ointment finally selected for application to this affliction—the area plan—meets with his qualified approval. It is his privilege to inquire, at this stage in the application of the remedy, whether there may not be flies in the ointment. The inquiry is, therefore, sympathetic and critical, but not destructively critical. There are those, who have a right to express themselves because of their training and experience or because of their personal interests at stake, that see or think they see these offensive diptera. It is our duty carefully and without undue prejudice thoroughly to examine the ointment.

"The area plan of bovine tuberculosis eradication, if I am correctly informed, is not in a strict sense imposed upon any area. The areas involved voluntarily and democratically elect to submit to the cooperative machinery of eradication.

The explanations for this submission to the imposition of a temporary and more or less apparent or real hardship are: (1) Bovine tuberculosis is a destructive plague of cattle and swine. (2) It is communicable to man, especially to infants, by way of milk. (3) The tuberculosis situation in the United States and with respect to our available weapons of combat warrants the drastic measures of the plan.

"As the speaker sees it, the situation in the United States is as follows: (1) Vast areas into which tuberculosis has been introduced and where it constitutes a menace to livestock and human health, but where it has gained very little headway; and more limited areas, but very important with respect to their livestock and human population, where the disease is rapidly approaching a status as alarming as that which confronts the British Isles and parts of Western Europe. (2) A people who boast of their independence and individualism—who have occupied from ocean to ocean the most favorable single agricultural area on the face of the earth and called it the "land of the free and the home of the brave," but who, most paradoxically, surrender their individuality and freedom of action with an abandon that baffles the psychologist.

"The examination of the ointment should be as painstaking as have been the procedures in its manufacture. Some of the dipteran masses may be only imaginary—in the eye of the critic and not in the ointment; some may be tiny black specks that should not and need not be tolerated, but are not of serious consequence; some may be real flies. Again there may be swarms of flies about the ointment-pot, threatening to get in and generally causing irritation."

There were then asked and answered some questions which we may some day be called upon to ask and answer with respect to brucellosis.

- (1) Is tuberculosis transmissible to man?
- (2) Is tuberculosis of livestock curable?
- (3) Is it preventable?
- (4) Is it possible to test cattle, swine, and poultry for tuberculosis and pick out all the affected animals and none of the non-infected?
- (5) Is it possible to perfect the technic of the plan?
- (6) Will the eradication of bovine tuberculosis incidentally mean the eradication of swine tuberculosis?
- (7) Will the eradication of tuberculosis from cattle only result in its permanent disappearance from cattle?
- (8) Are not owners of livestock and the general public led to the view that the success of the area plan means more to them than the facts warrant?
- (9) Has not the area plan tended toward a weakening of the fabric of veterinary pedagogy, science and practice?

It is not pertinent to quote the answers. Answers to similar questions concerning brucellosis would not be exactly the same but probably very similar. One needs to be warned against the assumption that, when disease eradication programs begin to operate, research programs cease. Not infrequently, the very good program, seemingly water tight, springs many leaks under the stress of operation. These leaks may make the best leads for investigational projects. Society cannot await the acquisition of all the ascertainable facts about a disease before utilizing those that are available and society should be cautious about tackling a disease eradication project with too meagre equipment.

In the latest report available Mohler (1931, p. 3) (143) sums up progress thus:

"The eradication of tuberculosis from cattle proceeded rapidly during the year and exceeded all former years in volume of testing. Two additional States—Michigan and Indiana—completed the testing of their entire areas and were officially designated as modified accredited areas, signifying the practical freedom

of their cattle herds from tuberculosis. This achievement, added to the accreditation of North Carolina and Maine, previously reported, gives further convincing proof of the effectiveness of the methods being used to eradicate the disease.

"Favorable public sentiment has been largely responsible for the successful progress made. Opposition to the work, though lately only of sporadic nature, was reduced further by several important court decisions rendered during the year. The accreditation of Michigan followed closely a decision of a circuit judge in that State sustaining the right of public authority to test, condemn, appraise, and slaughter privately owned cattle in the campaign to eradicate bovine tuberculosis. A decision of the Supreme Court of Iowa likewise was beneficial in advancing tuberculin testing in that State. The decision upheld the reliability and value of the test and the view that bovine tuberculosis is transmissible to human beings."

The armed resistance to the work in Iowa is frankly discussed by Malcolm (1932) (164) and it was fully reported in the agricultural press and various news services.

Very recently (1932) (165) we find a report of the aftermath of the resistance to tuberculosis eradication in Iowa:

"Two recent decisions in Iowa courts upheld the Iowa State law requiring the tuberculin-testing of cattle. In reporting the circumstances to the U. S. Department of Agriculture, Dr. J. A. Barger, B. A. I., inspector in charge of tuberculosis eradication in Iowa, says that in one case two farmers from Cedar County were sentenced to three years each in the Iowa State Penitentiary, at Fort Madison, and also were assessed the costs of the trial. These men were convicted by a jury in a Jones County court for conspiring to incite Cedar County farmers to resist the testing of cattle for tuberculosis.

"The other court decision denied an application by a cattle owner of Waterloo for a temporary injunction enjoining the Iowa Department of Agriculture from testing his herd of 44 dairy cows. The court declared that testing of cattle is a measure of public health and should not be delayed or stopped because of the remote possibility that a healthy animal may be condemned or the test found not infallible.

"These decisions are in keeping with four previous court decisions, before four different judges, in which the Iowa tuberculin testing law was upheld, according to officials of the U. S. Bureau of Animal Industry."

Annually a report is made on progress of the work to the U. S. Live-stock Sanitary Association. The proceedings of the association's meetings are published in the March number of the Journal of the American Veterinary Medical Association each year.

There are significant differences between tuberculosis and brucellosis so that, in spite of the many points of similarity we may not hope that an exact duplicate of the plan for attacking the former disease will be applicable to the latter. Birch (1932) (166) has placed in parallel the comparisons and the contrasts between the two diseases. Most students of the problem of animal disease eradication will accept his picture as reasonably accurate. The italics only are suggested by the writer to indicate the points of the contrast; obviously there is more contrast than comparison.

Tuberculosis

1. Specific infectious disease acquired by contact.
2. Chronic disease, usually spreads slowly, many months between date of exposure and time when animal becomes spreader.
3. Animals less than one year old highly susceptible, readily acquire permanent infection, and break down in later life.
4. Pregnancy exerts no influence on probabilities of spread.
5. No period of special danger of spread.
6. Tends to become progressively worse in the individual. Recovery not a factor as it relates to official measures.
7. Recently infected animals least dangerous to associates.
8. Because of relatively low and increasing prevalence reactors can be destroyed and the owners indemnified. Disposal of reactors is therefore a standardized procedure.
9. Immunity, tolerance and recovery play no part in the disposal of reactors.
10. There is a reasonably accurate test to identify infected animals, the tuberculin test.
11. The only effective method of control consists in establishing and protecting a clean herd through periodic testing.
12. "Once a reactor always a reactor" is sound policy in using the tuberculin test, though numerous false reactions occur.
13. One test interferes in greater or less degree with those made subsequently on the same animal.
14. Making all tests official may be accomplished fairly well through control of tuberculin.
15. There is need to make all tests official because one test modifies the accuracy of subsequent ones.
16. When doubt exists as to the accuracy of a test a purchaser, or a state receiving the tested animal, cannot always apply repeated retests.
17. No material is readily available which may be used to produce reaction in clean cattle which a purchaser may wish to reject.

Bang's Disease

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5. *Special danger of spread at time of parturition.*
6. *Destroys the value of many animals in a short time. Majority of those which remain gradually become tolerant of the infection and assume the outward appearances of immunity, but remain as carriers and potential spreaders. A few actually recover and cease to be carriers.*
7. *Recently infected animals most dangerous to their associates.*
8. *Because of a relatively high prevalence, which forbids indemnities, and to the high value as individuals of selected chronic reactors, handling of reactors is the most difficult individual problem which sanitary officials must face.*
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16. *An unlimited number of retests may be applied, and the same blood sample may be tested in several different laboratories.*
17. *Material is readily available which will cause a clean animal to react in approximately two weeks.*

Exception may be taken to items 11. The writer would not hold so rigidly to the thought that the *only* effective method of control in either disease is through periodic testing. This may not be the only method in so far as Bang's disease is concerned as will be shown in the discussions of vaccination, and it does not appear that it is *always* successful when given a reasonably fair trial.

A thorough study of the so-called area plan of cattle tuberculosis eradication in the United States and of the problems of brucellosis, especially of cattle, convinces one that this plan with appropriate modifications, might be adapted to brucellosis eradication more hopefully than any other procedure of animal disease eradication yet tested. But the tuberculosis eradication campaign may be said to have only fairly got under way. It was born only after a long and tedious gestation period and painful delivery; it has encountered natural difficulties inherent in the disease and the ignorance of those fighting it; it has met stubborn opposition of a small but irritated minority; it has had its day in court and on the battlefield; it has encountered difficulties in getting appropriations for inaugurating the work in some areas and in maintaining the appropriations for continuing the work after it has got under way. There is evidence that the success of the area plan has been fostered by the peculiar economics of the dairy situation. Not only has the dairyman realized that a tuberculous cow is as a rule not a good producer, is an actual or potential menace to his other cattle and hogs (to say nothing of his family), is a factor in lessening sales due to the public attitude toward tuberculous milk; but he has realized that in the interests of maintaining prices for dairy products the slaughter of very considerable numbers of milch cows may be more of a blessing than a blow to the industry.

The writer has interviewed many of those upon whom the burden would fall if a governmental brucellosis eradication campaign should be attempted. They are not in favor of inaugurating such a campaign. It may be said that they are fearfully opposed to such a move at this time. The writer shares this view with them.

It is well to feel the pulse of the layman who has much at stake in a problem of this character. Brucellosis has been much discussed in the lay press, especially in women's magazines and in the agricultural press. The hesitancy of the newspapers to discuss abortion has tended to keep the subject out of the daily news items and discussions of the press. There is certainly no unanimity of lay opinion relative to the problem of brucellosis. Typical of a considerable and influential group is the view of a well educated farm manager of Illinois, Mr. Allyn, (167) who expresses himself with more assurance than the facts warrant, "The end of bovine tuberculosis as an economic factor in animal husbandry is within plain sight in the United States. European sanitarians years ago believed it impossible to stamp this disease out of any country. Now we are nearly rid of it while Europe still has plenty. Our approach is different. We set a goal and reach it.

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The day may come when brucellosis will be attacked as tuberculosis is now, we hope, being conquered. In the meantime, much work must be done to prepare for such an attack or to cope with the disease in the absence of a governmental attack by less vigorous methods.

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Europe needs to be very vigilant in quarantining against the introduction of the infected milch goat into melitensis-free territory. Already, this infection has made some progress amongst sheep and cattle. The United States appears to have successfully guarded against further importations of *melitensis* infections. Especial attention should be given this matter in the southwestern states bordering on Mexico. In the absence of adequate statistical information relative to the prevalence of the disease in the goats of these states, it is premature to state dogmatically what mode of attack is to be recommended. Efforts should be made to prevent the interstate shipment of infected goats and the isolation and proper disposal of them should be considered.

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1. It is recognized that private or individual effort as a means of combating the disease is from the nature of the case inadequate;
2. Knowledge regarding the disease has reached such a point that it is possible to devise regulations which are likely to prove effectual if enforced by law;
3. The weight of opinion amongst those whose interests are affected by the disease is in favor of state control;
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Studies made here indicated that nearly everyone considered infectious abortion to be at that time (15 years ago) in the research stage. Perhaps half of those consulted thought that some educational or extension work might well be done. "The majority, while admitting that it is an infectious disease, would hesitate to treat it as such by regulatory measures until more accurate knowledge is available". The state accredited herd plan (to be discussed presently) did not seem feasible at that time.

In this paper the writer closed with this statement, "Livestock sanitary legislation or public health legislation in general should never attempt to direct the activities of public servants in detail, but the proper officials should be clothed with adequate powers enabling them to promulgate and to enforce regulations respecting any disease or condition that may exist under any set of circumstances. Such a system would demand only the highest types of public officials, only those who could be trusted absolutely. It is to such officials and to such a system that I look for relief in the control of abortion, but not until a vast outlay of money, time and energy (mental particularly) have been judiciously expended in studying the disease in an effort to answer the many unanswered questions about the disease."

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eral throughout the United States. Some states have created extension projects and provided veterinarians well versed in this disease to advise farmers through county agricultural agents of all phases of the disease. The committee found that 38 states have some plan for the control of Bang's disease. The general plan is based on the detection of the infected animals by the agglutination test and handling the reactors under the best possible procedure depending upon local conditions. Ten states report that no biological agents (vaccines, etc.) are used and 17 states report regulations for the control of the use of biologics. Thirty states have interstate regulations which prohibit the introduction of cattle unless they meet with certain requirements with respect to Bang's disease, 23 states definitely prohibiting the introduction of cattle unless they have passed a negative agglutination test. Seven states admit reactors by special permit or for immediate slaughter. It is advised that negative animals from an infected herd be quarantined and retested before being introduced into a negative herd. Consequently the buyer should be informed as to the condition of the herd from which he makes a purchase.

The increased interest in and better understanding of Bang's disease by the farmers and herd-owners has been responsible in a large degree for the decreased use of abortion remedies. The answers in the questionnaire thoroughly indicated that the use of abortion remedies is decidedly on the decline. Some states have passed laws prohibiting the use of abortion cures. Livestock sanitary officials in some of the states have waged a relentless war against these fake remedies.

Veterinarians throughout the country have in a large measure discontinued the use of abortion biologics. The use of abortion bacterins has decreased to a minimum. Live-culture vaccines are still being employed in treating Bang's disease to some extent. In some of the states, the use of live-culture vaccine is not permitted in a particular herd until the degree of infection is known and then this product is used only when it is deemed feasible.

During the past year, some of the states have passed regulations providing that only cattle negative to the abortion tests can be exhibited at state fairs. Some of the big national exhibitions of cattle have likewise adopted the rule that only cattle negative to the abortion test can be shown. Following the example of the states and national fairs, regional and county fairs have likewise passed similar regulations. Such regulations compel the owner of pure-livestock to make an early endeavor to rid his herd of this disease in the event that it is present.

Livestock owners seem to possess a keen appreciation of the devastating effects of this disease. Their interest is aroused to the point where they possess the desire to undertake a clean-out program. They appreciate at this stage that a pure-bred animal in the future will have little value unless it can be ascertained to be free of Bang's disease.

According to this committee report, the question of relationship of this disease to public health has held a prominent position. Considerable national publicity at one time indicated that Bang's disease was an important factor in public health. Careful research work has gone a far way in changing the original opinions of the seriousness of Bang's disease in human health. At the present time, there is sufficient information to indicate that Bang organisms in milk are rarely responsible for producing undulant fever in human. The exact extent to which this disease in cattle

is responsible for infecting human beings is not definitely determined and final decision on this particular point must await further reliable findings. It is apparent that the livestock sanitary officials minimize the effects that the bovine type of this disease has on the human family while the health officials tend to regard the bovine infection with more concern.

Some cities have passed or contemplate passing ordinances prohibiting the use of milk coming from infected cattle. Some ordinances tend to be more drastic than necessary, and as a result create an unwarranted burden on the herd owners.

Movements have been started in some states to provide funds for the purpose of not only eradicating this disease but also for providing indemnity where reacting animals are condemned and disposed of. Herd owners are inclined to support such a movement. Livestock sanitary officials at this time are definitely opposed to taxation for paying indemnity on abortion reactors. The amount of infection is so high, when compared to the amount of existing tuberculosis at its peak, that if operating costs and indemnity were paid, commensurate with that for tuberculosis eradication, appropriations to cover such costs and indemnity would have to be stupendous. In the eradication of Bang's disease from the herd, the owner must assume considerable responsibility relative to the execution of the sanitary program. A non-cooperative attitude would tend to stop progress against the disease in any herd. It is true that some animals which react to tests for Bang's disease may possess considerable economic value, and it would be contrary to policy to dispose of such animal for slaughter.

The question of the efficient detection of Bang's disease in cattle has received a great deal of attention. The agglutination tests (both the tube and the plate method) are regarded as being sufficiently accurate to be of great economic value. Comparative tests of many laboratories confirm that the plate method corresponds favorably with the tube method. Antigens used for the agglutination test may vary considerably. It is possible to produce a highly sensitive antigen or an antigen which can be regarded as lacking in sensitivity. The standard which is being used in most cases at the present time is the one which has been developed through experience in conducting a large number of tests and correlating the results of these tests with past and future histories of the cattle on which said tests were made. It is believed that different states employ somewhat different standards in relation to antigens used.

Experience has clearly indicated that the success which is achieved in eradicating this disease from a herd is dependent as much if not more upon the effectiveness of the sanitary procedure as it is upon the agglutination test. The results of an accurate agglutination test have little value if the application of these results through the sanitary program are not effective; since such is the case, it is important that a trained sanitarian, such as the practicing veterinarian, undertake the direction of the sanitary program. The practicing veterinarian should take an important part in the execution of the sanitary program and other phases of this disease.

In Wisconsin, practicing veterinarians, who are trained and approved for abortion control work, conduct the blood tests as well as direct the sanitary procedure; the work is checked from time to time and kept under close supervision. Only antigens, of which advance samples are approved by the state control laboratory, are permitted to be used, and all agglutination tests are compelled to be reported.

Research work has been in progress during the past year at the various experiment stations and the federal Bureau of Animal Industry in relation to the various phases of this disease. The Committee earnestly recommended that research projects pertaining to this disease be continued, and, if possible, be given more support. Research in connection with chemotherapy, biologics, improvement of antigens and the transmission and behavior of this disease under natural conditions, are particularly indicated.

* * * * *

The association refused to adopt the following recommendation of the committee (Malcolm) (172):

I. No dairy or breeding cattle shall be shipped, driven on foot, or otherwise transported interstate except upon the following conditions:

1. That such cattle are moved interstate to public livestock markets where federal inspection of livestock is maintained.

2. That such cattle come from a herd which has been officially certified as a Bang disease-free herd by the State in which the cattle originated.

3. Unless such cattle have been tested within 30 days prior to date of movement, by the agglutination test for Bang's disease, and shown to be free from such disease, such test not to be applied within 15 days from date of calving.

II. The rapid plate or tube agglutination test will be accepted providing it has been applied by a regularly employed state or federal veterinarian, or an accredited veterinarian who has had special instruction in applying the agglutination test by federal or state laboratory instructor, and approved by state livestock sanitary official.

III. Certificates of test charts must be made in triplicate form, one copy to be attached to waybill for shipment or otherwise movement of cattle. The two other copies must be forwarded by the veterinarian issuing same to the state veterinarian or sanitary official of the state where animals originate, for his approval and distribution. One copy is to be retained by him, one copy is to be forwarded to the livestock sanitary official in the state of destination.

IV. Each animal negative to the test shall be ear-tagged or otherwise permanently marked or identified by registration name and number.

The Committee suggested that the Committee for the following year formulate a uniform set of requirements for certification of Bang disease-free herds. This was done. The Committee report presented to the 1932 (December) meeting of the U. S. L. S. S. Association recommended that the Bureau of Animal Industry of the U. S. Department of Agriculture promulgate uniform regulations along lines laid down by the Committee. This recommendation was adopted despite the protestations of the representatives of the Federal Bureau (173).

* * * * *

It is apparent that there is a disposition among livestock sanitary authorities to make progress in dealing with Bang's disease but to proceed cautiously.

Success in the control of brucellosis of cattle is possible only if there is available a reasonably accurate diagnostic test. The committee on infectious abortion of the National Research Council, of which the writer was for many years a member, appointed a sub-committee to study the subject of standardization of the agglutination test for Bang's disease. The writer, as president of the Conference of State and National Research Workers in Animal Diseases, appointed Dr. C. P. Fitch, the chairman of the sub-committee, referee for the formulation of a standard agglutination test for Bang's disease. A report was made to the Conference and to the U. S.

Livestock Sanitary Association by Fitch in 1931 (174). This report was adopted by the latter association. It is too early to predict what effect the recommendations of this committee will have on actual uniform procedure in making the agglutination test. It is probable that many if not most laboratories will continue to make the test as in the past, but uniformity coupled with superiority or excellence will eventually prevail either by common consent or by compulsion.

The rapid plate method, or Huddleson test, is the official method in Michigan, Wisconsin, and a number of other states. Huddleson (1932) (175) has reviewed the work that has been done in the development of a rapid macroscopic agglutination test and has given a description of the method for making the antigen, a matter of the greatest importance, and for conducting the test. Donham and Fitch (1932) (176) have reported that in one out of 357 sera there is a delayed reaction in the rapid test. There is no explanation offered for these slow agglutinating sera which may delay the final reading until eight minutes instead of the usual two minutes. The authors state that there is no evidence to indicate that these delayed reactions are of sufficient importance to defeat the object of the rapid test.

Kolmer and Boerner (1931) (177) give a description of both the rapid test and the test tube test in their book prepared under the auspices of the American Society of Clinical Pathologists.

A study has been made in the laboratories at Cornell University of live culture antigens for the agglutination test. Milks (1931) reviews this work and reports on his experiments. He found that live antigen, standardized at 6 to 6.5 cm. on the Gates Opacimeter, was more uniform in its results than the carbolized antigen. Also the live antigen requires only six hours' incubation with overnight refrigeration, while the carbolized antigen requires 48 hours' incubation. There are so many obvious objections to a live culture antigen that it would have to be markedly superior to the killed cultures to warrant its adoption as a part of routine procedure.

Bovine Abortion Control Project for Michigan

The legal basis for regulatory work in the control of Bang's disease in Michigan is found in the following:

REGULATION REQUIRING TEST FOR BOVINE INFECTIOUS ABORTION ON CATTLE IMPORTED INTO MICHIGAN AND TO CONTROL INTRASTATE MOVEMENT OF CATTLE INFECTED WITH INFECTIOUS ABORTION

By virtue of the authority conferred upon the Commissioner of Agriculture under the provisions of Act 181 of the Public Acts of 1919, as amended, the following rules and regulations relating to the Abortion Disease of cattle are established to become effective on and after July 1, 1930.

1. Abortion Disease, Bovine Infectious Abortion or Bang Bacillus Disease shall mean the disease wherein an animal is infected with the Bang bacillus (*Brucella Abortus*), irrespective of the occurrence or absence of an abortion.

2. An animal shall be considered infected with Bang bacillus (*Brucella Abortus*), if it gives a positive reaction to any test for Bovine Infectious Abortion recognized and approved by the Michigan Department of Agriculture; or if the Bang bacillus (*Brucella Abortus*) has been found in the body or its secretions or discharges.

3. Animals infected with Bovine Infectious Abortion as herein defined shall not be sold, traded, given away nor removed from the premises except under permit from the Michigan Department of Agriculture. Permits for the removal of in-

fectured animals will be issued only under the condition that their destination shall be immediate slaughter or that they be placed in infected herds.

4. In each and every instance where animals defined herein as infected are sold, traded, given away, removed to other premises, or offered for sale the owner or his agent must represent such animals as infected. Before any cattle which have been vaccinated with living Bang bacilli are sold or moved from the premises of the owner, said owner or his agent, shall notify the prospective purchaser, or owner, or owners of cattle, with which such cattle will come in contact, that such cattle have been so treated, giving the date of treatment.

5. All dairy or breeding cattle over six months of age entering the State of Michigan in any manner, except cattle from herds officially certified to by the Livestock Sanitary officials of the state of origin as free from Bovine Infectious Abortion, must pass an agglutination blood test approved by the Livestock Sanitary official of the state of origin within thirty days prior to importation, provided such test shall not be recognized if made within five days before or fifteen days after calving. The date of test and results must be shown on properly executed certificates. Copy of such certificates should be attached to the waybill and another copy forwarded immediately to the State Veterinarian at Lansing, Michigan. Provided, further, that this section shall not be held to apply to cattle moved into the State of Michigan for feeding and grazing purposes and kept segregated from dairy and breeding cattle during the feeding period; nor shall this section apply to cattle moved into the State of Michigan for exhibition purposes but in the event that exhibition cattle are sold to remain in the State of Michigan, or are retained by the owner in Michigan longer than sixty (60) days, such cattle shall be subject to an agglutination blood test approved by the Michigan Department of Agriculture. Cattle infected with Bovine Infectious Abortion as herein defined shall not be brought into Michigan except for immediate slaughter or under permit from the Michigan Department of Agriculture for entry into specified infected herds.

6. It shall be the duty of any person making any blood tests, or other diagnostic tests for Bovine Infectious Abortion, to report such tests in writing to the Department of Agriculture at Lansing, Michigan, within five days after the completion of such tests. Each report shall be signed by the person who shall have made the test and shall contain a complete statement of the actual results of the test; the name and address of the owner or person in control of the animals tested; and the identification of each animal tested by means of ear tag numbers, registration numbers or tattoo numbers.

7. No person shall inject or otherwise administer to any livestock any substance containing, or purported to contain, living Bang bacilli (*Brucella Abortus*) except upon specific written permission to do so from an authorized representative of the Michigan Department of Agriculture. The holder of a permit to administer vaccine for the treatment of Bovine Infectious Abortion shall submit a report to the Department of Agriculture, Lansing, Michigan, within ten days showing a record of each animal so treated, the name and address of the owner or person in control of the animals treated, and the name and address of the manufacturer of the vaccine used.

8. Any person, firm, or corporation selling or delivering any product containing or purported to contain, living Bang bacilli for the purpose of vaccination and Bang bacilli antigen for the purpose of testing, within the State of Michigan shall within five days report such sale or delivery to the Commissioner of Agriculture, Lansing, Michigan, specifying in such report the date of sale, the name and address of the purchaser, or consignee, and the quantity of the product sold or delivered.

In witness Whereof, I have hereunto set my hand and affixed the seal of the Department of Agriculture in the City of Lansing, State of Michigan, this twentieth day of May, Nineteen Hundred and Thirty.

SEAL

HERBERT E. POWELL,
Commissioner of Agriculture.

In order to encourage the cattle owner to free his herd of Bang's disease and officially to recognize the *fait accompli*, the Michigan State Department of Agriculture has outlined the following:

RULES AND REGULATIONS FOR THE ESTABLISHMENT AND
MAINTENANCE OF ABORTION FREE HERDS OF CATTLE

1. An Abortion Free Accredited Herd is one in which no evidence of bovine infectious abortion has been found in three blood tests, at least six months apart, of all cattle, including all calves, in the herd.
2. The owner must place his herd under the supervision of the Michigan Department of Agriculture for the prevention, control and eradication of Bovine Infectious Abortion.
3. A list of cattle shall be furnished each time a test is applied so that each blood sample can be identified by name and registry number, ear tag number or tattoo number.
4. Premises on which an Abortion Free Accredited Herd or a herd in the process of accreditation is maintained must be kept in a sanitary condition.
5. All reacting animals shall be removed from the herd immediately and maintained in quarantine separate from non-reacting cattle or shipped for slaughter.
6. Retests of herds in which reactors are located shall not be made earlier than thirty days nor later than six months after the date of last test of such herds.
7. An Abortion Free Accredited Herd shall be retested at least annually. If one reactor to the blood test is revealed in such herd and there is no visible evidence of the spread of the disease, the reactor shall be removed and the certificate held in suspension. If at a subsequent blood test of the entire herd in not less than thirty days, no additional reactor is revealed, the certificate may continue in effect. If more than one animal in a herd certified as Abortion Free reacts to the blood test, or if one or more animals abort and is infected with the Bang Bacillus as determined by the blood test or otherwise, the certificate shall be void and the herd must requalify.
8. If an abortion occurs in a herd certified as Abortion Free, it must be reported immediately to the Michigan Department of Agriculture, and the aborting animal must be isolated promptly. The place where the abortion occurred must be cleaned and disinfected at once and the fetus and membranes burned or properly buried.
9. Herd bulls must not be used for service on cattle which have not been blood tested and found free from Bovine Infectious Abortion.
10. All milk and milk products fed to cattle in an Abortion Free Accredited Herd, or in a herd in the process of accreditation, shall be produced by an approved herd or shall be properly pasteurized or boiled.
11. Cattle from an Abortion Free Accredited Herd may be added to such herd or herds in the process of accreditation without test, provided they are moved in such a manner as not to be exposed to infection. If shipped by railroad or truck, the vehicle must be cleaned and disinfected in advance. Public stock yard must be avoided. The Michigan Department of Agriculture must be notified immediately when cattle are added or returned to an Abortion Free Accredited Herd or a herd in the process of accreditation.
12. Cattle, except calves under six months of age, to be added to an Accredited Herd or herd in the process of accreditation, other than cattle from an Abortion Free Accredited Herd, must pass a negative blood test and then must be isolated until they have passed a second blood test made not earlier than sixty days after the first date of isolation. Calves under six months of age may be added after having passed one negative test.
13. Cattle removed from an Abortion Free Accredited Herd or a herd in the process of accreditation for exhibition or other purposes shall not be returned to such herd until they have been held in isolation for a period of sixty days and at the end of that time have passed a negative blood test.
14. Blood tests shall be made by the Michigan Department of Agriculture laboratory and said Department reserves the right to supervise or direct the collection of any or all blood samples.
15. An Abortion Free Accredited Herd certificate shall be issued to owners of herds which have qualified according to paragraph one, provided the requirements of these rules and regulations and the agreement executed by the owner are met. Such certificate shall be valid for one year from date issued unless cancelled.

The herd owner signs the following :

AGREEMENT FOR THE ACCREDITATION OF ABORTION FREE
HERDS OF CATTLE

Whereas, The State Department of Agriculture of Michigan, for the purpose of encouraging and maintaining herds of cattle free from the Abortion disease and promoting the interchange of healthy cattle, propose insofar as possible to co-operate with breeders of cattle to assist them in eradicating Abortion disease from their herds and to maintain Officially Accredited Free Herds.

Now, Therefore, In consideration of the cooperative assistance of the State Department of Agriculture for the purposes specified, I,

..... hereby agree to cooperate with said Department of Agriculture and will have my entire herd of cattle, or any cattle of my herd examined and tested at such times as the State Department of Agriculture may deem necessary. All blood samples, examination of which is intended to aid in determining the existence or absence of abortion disease in any of the cattle of my herd, shall be drawn by a Veterinarian approved by the State Department of Agriculture and shall be submitted to the State Department of Agriculture Laboratory for examination.

I further agree that I will handle and control my herd of cattle, or any part thereof, in conformity with the Rules and Regulations of the State Department of Agriculture relating to accreditation of Abortion Free Herds now in force, or which may hereafter be promulgated, concerning the eradication of Abortion disease under the State Department of Agriculture Accredited Herd plan.

I further agree, and I understand that the handling or control of my herd of cattle, or any part thereof, not in conformity with the rules and regulations of the State Department of Agriculture established for the purposes hereinbefore stated shall upon notice, and a hearing before the Commissioner of Agriculture, subject any certificate pertaining to the before mentioned agreement to cancellation.

My herd is composed as listed below :

Predominating breed		
Number of Cattle	Pure-Bred	Grade
		Total

In Witness Whereof, I have signed this agreement this day of One Thousand Nine Hundred and

..... Owner

Address

Witness

It is recognized that no movement so stupendous as the eradication of an insidious and widespread disease of cattle can be successfully attacked by law or regulation alone and that law and regulation are futile in a democracy in the absence of widely diffused knowledge concerning the nature of the problem. To translate the cold laboratory facts of research concerning Bang's disease into live, meaningful and applicable barnyard facts has been the project of the Extension Veterinarian of the Department of Animal Pathology of Michigan State College. The field project was started in March, 1930. Dr. E. T. Hallman, head of the Department, and Dr. B. J. Killham, Extension Veterinarian, have outlined the following project :

PLAN OF WORK FOR BOVINE ABORTION CONTROL STATE OF MICHIGAN

I. Situation.

1. The abortion disease (Bang's disease) has a very important bearing on profitable dairy and beef production. It is probable that the average cow affected with this disease causes an annual loss to its owner of approximately \$40.00 due to lowered productive ability, loss of calves, sterility, and depreciation. The loss to the Dairy Industry of Michigan alone is enormous. It is estimated that 15 per cent of the cattle of the State are affected with this disease. There are approximately 860,000 dairy cows and heifers in Michigan. If 15 per cent of this number, or 129,000, are affected with the disease and the loss is \$40.00 per cow per annum, abortion disease is costing the dairy farmers of Michigan more than \$5,000,000.00 each year. Assuming that the contention that this disease has increased 100 per cent in the last decade in the absence of concerted control efforts is correct, the outlook under existing conditions would be extremely discouraging to the cattle owner.

2. The losses caused by the abortion diseases are due not only to the actual abortions but to retained afterbirths, breeding difficulties, udder disease, and pneumonia and scours in calves. The breeding difficulties frequently assume the form of permanent sterility. It is largely because the average cattle owner views this disease from the aspect of the abortions only that many of the alleged cures and remedies are sold.

3. Although the public attitude toward the milk from cows affected with the disease may not be entirely justified in view of the apparently demonstrated fact that contact and association with diseased animals is a more important factor in the transmission of undulant fever to the human being, such attitude and the resulting agitation has required and will require some action toward control measures.

4. Approximately two-thirds of the states of the Union have now prohibited the importation of cattle affected with the abortion disease, and the best market for surplus Michigan cattle is in other states. No dairy or breeding cattle can now be shipped to any state immediately adjoining Michigan without passing a satisfactory blood test for Bang's disease, and New Jersey, the largest purchaser of Michigan cattle, now has a similar requirement. A rapidly increasing number of cities and villages are regulating against milk from infected cows with the disease. Pure bred cattle organizations and discriminating individual buyers are specifying that cattle must pass the blood test for this disease. The possibility of cattle contracting the disease at fairs and exhibitions has been emphasized, and it appears that in the not distant future demands for protection against the disease at various types of sales including ordinary farm sales may be expected. Undoubtedly much spread of the abortion disease occurs through lack of knowledge of the dangers in connection with sales, exhibitions, and other activities which permit or include movement or contact of cattle.

5. No chemical or biological agent can be offered at this time as a cure or control for Bang's disease, but the disease can be controlled and eventually eradicated from herds by the use of the blood test, segregation or slaughter of diseased animals, and the application of sanitary principles. The situation is complicated, however, by the average farmer's lack of understanding of the fundamentals of sanitation and the necessity of demonstrating to him the ways by which practical segregation can be accomplished. Additional obstacles are presented by the failure of many veterinarians to grasp the true situation. Some are advocating the use of such biological agents as bacterins, serums, and vaccines although the two former have been declared to be valueless and the use of the latter has been condemned by the American Veterinary Medical Association, and the United States Livestock Sanitary Association, the two largest existing organizations interested in the control of animal diseases. Commercial literature and other propaganda are responsible for much of this trouble, and such efforts will have to be neutralized.

6. The State Department of Agriculture is conducting blood tests without charge to the cattle owners.* Some veterinarians are making blood tests and others are desirous of doing so. Obviously the veterinarian can not do this work for nothing, and, although his qualifications may be ample, he must depend upon commercial

*Since Aug. 1, 1931, a fee has been charged for conducting the test. This has not resulted in any material reduction in the number of tests conducted.

antigen for use in connection with the test, and such antigen is not yet satisfactorily standardized.

7. With progress in control efforts in individual herds comes the realization of the need of disease free herds to which the owners of infected herds can go for replacement animals. Although the response has been gratifying and the progress satisfactory, sufficient time has not yet elapsed to permit herds to qualify for accreditation.

8. The increase in the number of blood samples tested for farmers of the state may fairly be assumed to indicate the growing interest in efforts to control the abortion disease of cattle. The laboratory reports reveal the following information in this respect:

Month	Year 1929			Year 1930			Year 1931			Year 1932		
	Neg.	Sus. and React.	Per cent of Sus. and React.	Neg.	Sus. and React.	Per cent of Sus. and React.	Neg.	Sus. and React.	Per cent of Sus. and React.	Neg.	Sus. and React.	Per cent of Sus. and React.
January....	1123	293	20.5	1497	576	27.3	3428	601	14.9	1940	340	14.9
February...	1222	576	31.9	1774	729	28.8	2880	615	17.5	2170	331	13.2
March.....	1134	571	33.2	2165	1110	34.	2959	441	12.9	2797	316	10.1
April.....	1029	469	31.0	2167	909	27.4	3343	654	16.3	3467	395	10.2
May.....	1047	444	29.6	2401	582	19.3	3758	694	15.5	3691	572	13.3
June.....	1037	358	25.3	2060	539	20.6	2728	506	15.6	1737	328	15.9
July.....	890	576	39.1	1791	626	25.1	2802	474	14.4	2674	417	13.5
August.....	976	605	38.0	1460	413	18.5	2446	561	18.6	2459	392	10.2
September..	955	428	30.4	2072	392	15.9	3385	518	13.2	2562	333	11.5
October.....	1335	472	25.9	2796	845	23.1	3454	512	12.9	2902	358	11.0
November..	2111	626	22.3	2359	578	19.6	2418	583	10.4	3530	510	12.6
December...	1569	516	24.5	2548	435	14.5	3141	565	15.2	3396	417	10.9

The preceding chart* shows the results obtained in the routine testing (rapid macroscopic method) of all bovine blood samples received at the Department of Agriculture Laboratory for the diagnosis of Bang's disease during the years 1929-32 inclusive.

A cursory examination shows an irregular variation in the number of animals showing suspicious and positive reactions from month to month though a steady general lowering in number of this class. There are a number of factors not evident on the chart involved in the production of these seemingly wide variations. Chief of these factors which should be mentioned are the repeated tests of infected herds, the omission in certain months of State institution herd samples (most of which are negative) and

*I am indebted to Dr. Don R. Coburn for aid in making and interpreting this chart.

seasonal variation in interstate shipments of cattle. There is also a seasonal variation in the make-up of farm herds as young cattle on pasture are seldom tested during the months when grazing is possible.

The latter months of the year 1930 and those following show a sustained lowering in the per cent of infection, reflecting the results of the work of Dr. Killham, extension veterinarian, in the introduction of many new negative herds to the demonstration and accredited herd lists. The repeated tests of herds in the process of accreditation have also materially influenced the reduction shown and should be given proper evaluation with the other factors mentioned when comparing the 20.5 per cent of infection of January, 1929 with the 10.9 per cent of December, 1932.

Blood Samples received for testing during 1929-1932

Month	1929	1930	1931	1932	Month	1929	1930	1931	1932
January.....	1429	2111	4046	2282	July.....	1474	2497	3295	3093
February....	1805	2532	3507	2508	August.....	1591	2228	3015	3857
March.....	1722	3307	3410	3115	September...	1407	2472	3911	2903
April.....	1511	3313	4007	3869	October.....	1824	3654	3974	3264
May.....	1498	3008	4480	4287	November...	2808	2947	3012	4041
June.....	1414	2613	3241	2067	December...	2109	2991	3715	3821

II. Phases of Project.

1. Continue the introduction of project into every county of the State through meetings of farmers and veterinarians.

2. Addressing larger meetings of cattle owners and breeders and persons interested in animal and dairy husbandry insofar as practicable for purpose of discussing abortion disease problems.

3. Group meetings of farmers for purpose of outlining procedures with reference to cleaning up herds and keeping clean herds clean. At these meetings efforts will be made to stimulate interest in blood testing, advise as to methods of segregation and emphasize the importance of fundamental sanitation.

4. Establishment of demonstration herds in each county if possible and particularly in localities where the abortion disease is very prevalent for the purpose of showing what can be accomplished through the use of the blood test, segregation or slaughter, and sanitation. This work to be followed through and the herd owners in each instance advised and encouraged to continue until definite results are demonstrated.

5. Instructing, directing, and cooperating with veterinarians.

6. Promoting closer cooperation between farmers and veterinarians.

7. Cooperation with State Department of Agriculture in matters relating to abortion disease control, this activity to include efforts to establish herds as Abortion Disease Free Accredited Herds.

8. Rendering assistance in preventing spread of abortion disease through operations of bull rings or community bull projects.

III. Goals for Year.

1. Continue discussion of project in more important cattle counties of state and particularly in those counties where the disease is most prevalent.

2. Continue presentation of project and views regarding control of Bang's disease to veterinarians and others, and advise veterinarians individually and collectively relative to developments and details of procedures.

3. Establish more demonstration herds and continue supervision of the 145 herds with which work has been started.

4. Group meetings appear to present the best opportunity for close contact with the cattle owner, and this type of meeting will be advocated when and where possible.

5. Continuing work, with the 64 herds now in process of accreditation with a view to having at least 25 of the number accredited.

6. Instructing veterinarians regarding efficient and proper bleeding of cattle and other necessary procedures.

IV. Extension Methods.

1. Introduction of project into the various counties to be accomplished through meetings of farmers arranged for by the county agricultural agents, through meetings of veterinarians called by the county agents, and through local veterinary associations.

2. The project will also be presented to the various breed associations, shipping associations, creamery associations, and similar organizations.

3. Closer contact with breeders and veterinarians for purposes of more detailed instruction and supervision to be had through small group meetings of farmers and personal interviews with cooperating veterinarians. The extension specialist will cooperate with other specialists of the Extension Division, especially those in dairy and animal husbandry.

4. The selection of demonstration herds will be made by the extension specialist and county agricultural agent, and together with the owner of such herds, a practicing veterinarian satisfactory to the cooperating parties will be selected to perform the necessary professional service required in the operation of the demonstration herd.

5. The extension specialist will be responsible for the methods adopted and operation of the project.

V. Calendar of Work.

The project is a year around one. In the fall and winter larger meetings, interspersed with demonstration herd work will be emphasized because of the greater amount of leisure breeders have at this time. In the spring and summer more emphasis will be placed on small group meetings, work with veterinarians, and demonstration herd work.

VI. What County Agricultural Agents Will Do.

The county agent, being the representative of the Extension Division (of Michigan State College) in his County, will be the local leader of the project in the county. Meetings of breeders and veterinarians will be arranged for by him. He, with the assistance and consent of the extension specialist, will be responsible for the selection of demonstration herds and the two with the assistance and consent of the owners of such herds will select the cooperating veterinarian to be in charge of the technical veterinary work in the operation of the demonstration herd. From time to time group meetings on the demonstration farms will be arranged for by the county agent to discuss the problems and progress of the work. The county agent will be responsible for giving the project the necessary publicity in his county.

VII. Literature.

1. An extension bulletin on Bang's Disease (1931) (178), has been published, but the available copies are moving rapidly. If the supply becomes exhausted, slight revisions will be made and a reprint requested.

2. A brief but comprehensive outline of the Bang's Disease problem will be prepared for distribution particularly to owners of demonstration herds.

3. Items of interest and notes on progress will be published for distribution when such material is available. Extension workers will be supplied with material for publication.

4. Charts have been prepared for use in both the lower and upper peninsulas, and these will be revised and augmented from time to time.

5. When sufficient progress can be demonstrated, a periodical bulletin showing mass and individual progress and discussing developments and new procedures will be advocated.

VIII. Measuring Results.

Results will be measured with reference to goals when possible, but it may be difficult to evaluate results with any degree of accuracy. The increase in attendance and interest at meetings has been most pronounced as the work proceeds, and continuation of these features should indicate progress. Increased interest on the part of farmers, veterinarians, and others as indicated by correspondence, interviews, and requests for meetings will be considered as evidence of advancement. Requests for assistance in establishing demonstration herds and inquiries regarding the plan for accreditation of herds as free from the disease should be taken as indications of results. The increase in the number of diseased cows shipped for slaughter and desire of the farmer to be protected against the disease at sales and fairs and through breeding operations are evidences of knowledge acquired regarding the disease and may be used as barometers. The increase in the number of blood samples submitted for test very clearly shows increased interest. The actual cleaning up of infected herds and the definite establishment of accredited herds can be definitely gauged.

Killham (1932) (144a) reported that by 1931 the plan had affected a total of 227 demonstration herds containing 4,655 cattle and that 34 infected herds had been cleaned up during year, while at the close of 1932, 368 herds and 7,329 cattle had been involved and that 66 herds had been cleaned up. In addition, of course, some herds which had not been completely rid of the disease had made progress. The failures appeared to be less than five per cent and some of these were due to such causes as the type of owner, mismanagement, and poor facilities. Calls were made in company with the chief milk inspector of Grand Rapids on herd owners whose herds had been blood tested because of a recently enforced ordinance relating to raw milk. The Detroit Stock Yard company was induced to erect a large barn to hold cattle under test since all dairy and breeding cattle must pass a negative test before they can be removed from the stock yards.

Killham admits that the plan for accreditation does not, and probably will not, appeal to a large number of Michigan herd owners, and in many instances it is not recommended. The rules are rigid and the possible reward for the owner of a small grade herd may not appear inviting; but the advantages to the owner of a pure bred herd, a high producing herd, a herd supplying raw milk to a city or village, or a herd from which the owner hopes to make advantageous sales are great, and the owners of such herds are urged to consider the plan.

Several other states, notably Pennsylvania,* have been working with similar projects for a longer or briefer period. These projects are valuable as precursors to any concerted governmental control or eradication program or they may serve in lieu of such a program for many years to come. Practical experience with such projects shows that they have severe limitations. In the first place, only relatively small numbers of herds have been brought under the operation of the plan during a considerable period of time. Next, as indicated in the Michigan plan, a considerable percentage of those with whom cooperative efforts are attempted fail to develop the cooperative spirit or cooperation is impossible for economic or other reasons and the work is discontinued. Again, we have encountered a

*This has been called the Pennsylvania plan, or by the name of some other state. It is really only a modification of the Bang system suggested for the control of tuberculosis of cattle.

significant number of cases in which, in spite of persistent application of the method and apparently cordial cooperative spirit and practice and when economic considerations have not been paramount, the disease has not disappeared and the owner has sought an alternative approach.

Finally, the matter of continued susceptibility, if not eventually of increased susceptibility in the absence of the immunizing agent, the pathogenic *Brucella*, and the constant danger of ever recurring infection pending the complete disappearance of *Brucella* are objections to the eradication plan. A herd owner may be surrounded by infected herds. If he maintains a *Brucella* free herd while his neighbors maintain *Brucella* infected herds, what is to prevent the introduction onto his premises of infective material by visitors, dogs, cattle breaking through insecure fences, and defects in the scientific basis and official practices of control? It seems clear that the eradication of infection does not promote immunity. There developed such prominent symptoms of intolerance to any alternative plans of control that the writer (1933) (180) took occasion to discuss the matter in extenso before the 1932 meeting of the U. S. Livestock Sanitary Association.

Vaccination The control of Bang's diseases by the use of preventive biologic preparation has been attempted. The most rabid proponents of eradication decry all such methods as temporizing with something inherently bad and not to be tolerated by intelligent society. Perhaps there are microbial diseases that can be relegated to the closed chapters of history. Perhaps brucellosis is such an infection or infection group. Without discounting the efforts of those who would make *Brucella* cultures available only in bacteriological laboratories, the writer belongs to the group that would either welcome a safe and effective immunizing agent or accept it if, when, and as repressive measures fail.

Reference has already been made to chemotherapy in the treatment of human brucellosis. It does not appear hopeful as a curative possibility and appears much less hopeful as a preventative. Serum therapy is theoretically out of the question as a preventative, since at the best it would give only a passive immunity and then only at prohibitive expense, and researches have yielded very little to encourage animal husbandry to expect anything from it even as a possibility. Bacterins or killed cultures have not proved effective. There are numerous references in the literature to their use. We have experimented with them with discouraging results (1916) (181). A method has not been perfected to devitalize *Brucella* without denaturizing it with respect to its immunizing antigenic properties. It seems that resort must be had to a live culture vaccine.

Huhtala (1931) (182) of Finland has had the same experience with biological preparations that others have had in both America and Europe. He made his observations in heavily infected regions in which about 25-35 per cent of all cattle were infected with *Br. abortus*. Individual farms had 15 to 40 cows. These properties were exclusively devoted to milk production; since in these circumstances, destruction of the infection was practically impossible, methods were chiefly directed towards maintaining production. It appeared that introduction of the plague into healthy herds was principally by indirect ways; therefore it seems that the epizootic in the early stages is insidious. With this in mind, diagnosis was established in this stage and campaign measures begun. Strict accomplishment of systematic hygienic measures was of greatest value. Immunization with killed

cultures did not give satisfactory results. On the contrary, inoculation of living cultures subcutaneously gave very good results. The author described in detail his method of dealing with control of infectious abortion in dairy herds. In Finland, there is compulsory notification and pasteurization of *Br. abortus* infected milk.

Huddleson (1920) (183) isolated from an aborted bovine fetus a strain of *Br. abortus* that proved to be innocuous to guinea pigs by either injection or ingestion. He (1924) (184) published on the favorable results of the use of this strain as a vaccine for cattle. Five years later (1929) (185) he reported on further studies along the same line. Since that date, the work has been pushed through cooperation with Parke, Davis, and Company and with the Bureau of Animal Industry of the U. S. Department of Agriculture. Giltner and Huddleson and Clark and Schlingman of Parke, Davis and Company (1929) (186) summarized the results of all the tests up to the time of the inauguration of the cooperative work with the B. A. I. in these words:

"The injection of the living non-virulent strain of *Br. abortus* in the form of a vaccine into cattle both pregnant and non-pregnant produces no harmful results.

"The injection of the vaccine into negative animals in two of the series of field tests brought about a striking reduction in the abortion rate in these animals over a period of from one to three years. In the other series, in which negative controls were maintained, there was not a wide difference in the abortion rate between the treated and control animals.

"It has been conclusively determined that experimental animals can be protected against massive artificial infection for a period of over two years.

"The vaccine must still be considered in the experimental stage and further well-controlled tests should be made to determine its value as an agent for protecting cattle against *Br. abortus* infection."

These data emphasize the fact that the efficiency of an immunizing agent against Bang's abortion disease should be determined on the basis of the presence or absence of infection rather than on the presence or absence of the most conspicuous symptoms of the disease in the treated animals.

In the annual report of the veterinary division for the year ending June 30, 1930, Huddleson (1930) (136) recorded that on July 1, 1929, a field project was begun, in cooperation with the Bureau of Animal Industry of the U. S. Department of Agriculture, to determine the immunizing value of a nonvirulent, non-agglutinin producing, living culture of *Brucella abortus* (Bang). The field project is in charge of Dr. D. B. Meyer. The report for the year's work shows that 1.18 per cent of the 593 treated animals aborted, 2.07 per cent of the 242 negative controls aborted, and 3 per cent of the 266 positive untreated cattle aborted.

In the annual report of the veterinary division for the year ending June 30, 1931, Dr. Meyer (135a) states that the present data show conclusively that the vaccine produces no harmful results, the breeding efficiency of the animals is not reduced, the milk production is not lowered and the vaccine strain does not establish itself in the inoculated animal. It has not yet been determined how many doses, what size of dose, and what interval between injections will give the best results. It is not known very definitely how long the immunity will last hence it will require further experimentation and observation to establish the periods for re-vaccination. The vac-

cine will not, of course, alter the course of an infection already in progress, hence animals in infected herds in the incubative stage and the infected animals that fail to react to the agglutination test may abort or develop other manifestations of brucellosis in spite of vaccination. Experience with Huddleson's vaccine has demonstrated that it is not harmful, that it apparently has protected exposed herds from further infection, that an infected herd after treatment may be entirely rid of the infection and show no significant blood serum agglutination titer or any signs of infection. Huddleson's vaccine has been used on herds that have failed to respond satisfactorily to the testing and segregation plan.

Smith and Little (1923) (187) were among the first to study vaccination in this country. In a statement preliminary to detailing their experiments, they write, "A detailed study of unrestricted infectious diseases among domestic animals would be so costly as to be unjustifiable. Epidemiological laws must be worked out by interpolation of fragmentary data derived from various infected foci before means of suppression have become available. In the case of bovine infectious abortion two such methods present themselves. The infection may be eradicated by a destruction of all aborters and carriers or the resistance of the animals may be increased artificially by vaccination. It is towards the second problem that the following experiments have been directed. No attempt is made in this report to discuss the first problem and therefore no attitude is taken for or against either method of suppression. The second problem was chosen because it was the one that was open to attack under the conditions prevailing. The first method, that of elimination, is relatively simple in view of the high degree of accuracy of the agglutination test, but it is likely to prove very costly."

They reviewed the scanty literature on vaccination with respect to large herds in which natural exposure served as the test of resistance. They used two live *virulent* cultures as vaccines and they were able to demonstrate that the treatment had marked protective power as determined by the lowered abortion rate in the vaccinated animals. On the basis of the standards set up by use of Huddleson's vaccine we should consider their results as characterized by grave shortcomings. They were obviously not on the right track.

Hart and Traum (1925) (188) reported on vaccination studies in which the immunity of the treated animals was subjected to the test of artificially controlled infection. They too used virulent cultures and demonstrated not only their immunogenic powers, but also their fatal defect, the power to establish themselves in the udder of the lactating cow. Such a cow would be a spreader and thus dangerous in a herd of non-immunes and a menace to human health.

Carpenter (1926) (189) also showed that cattle vaccinated with living virulent cultures of *Brucella* have udder infection in a high percentage of cases.

Lubbehusen et al. (1926) (190) demonstrated that some degree of immunity is produced by the use of a living vaccine but they evidently were not satisfied with their results since they concluded that the only way with our present knowledge to successfully control the disease is on the basis of the clean herd as demonstrated by the serum test.

Wall (1926) (191) of Sweden has studied vaccination from a scientific point of view. A study of his experiments convinces one that there is yet

much to learn about the mechanism of immunity production in brucellosis with respect to the value of dead cultures, the choice of a strain of *Brucella* for live culture vaccination, the proper procedure for inoculation, size of dose, condition of animal (age, pregnancy, etc.), duration of immunity, and other points.

The investigators of the Bureau of Animal Industry of the U. S. Department of Agriculture have persistently studied vaccination against Bang's disease. Schroeder (1922) (192) reported that their work had been restricted to the use of killed cultures on pregnant and living cultures on non-pregnant cattle. The use of the living organism seemed to be attended by no unfavorable results and was followed by a slightly lessened abortion rate in a large badly infected private herd. In an experiment involving a small number of animals the investigator was satisfied that a live culture vaccine had marked protective power.

Cotton and Buck (1931) (193) reviewed the activities of the Bureau on this subject for the intervening nine years. They pointedly remarked, "Vaccination, though an unpopular subject with many, is, nevertheless one that cannot lightly be dismissed until it has definitely been proved to be incapable of being made to serve a useful purpose with safety to man and animals, or is shown to be a useful instrument with which to attack the abortion problem, a problem so great and with so many fronts that all the weapons that can be made available are needed for success in combating it." Again, "It is not our purpose to belittle the efforts at eradication by blood tests, elimination and segregation of reactors and sanitary measures. Such methods, where they can economically be used, are better by far than any vaccination program. But there are very many in which even a moderately efficient vaccine, if reasonably safe, could be used to advantage". They studied calfhood vaccination with encouraging results. They point out the possibilities of calfhood vaccination as a means of meeting the objection to the use of virulent live cultures on adult milk producing cattle. They experimented with a comparatively avirulent strain and were able to afford some protection to the treated animals. In tests with vaccines of different degrees of virulence, they were able to conclude that highly virulent strains are decidedly objectionable even on unbred heifers because of the danger of implanting the infection in the udder. They were able to get very satisfactory results by the use of vaccines of lessened virulence not only with respect to the prevention of abortion, but also the absence of udder infection.

Cotton and Buck (1932) (194) made another report on their vaccination studies a year later. They concluded that: "While the results of our experiments have thus far failed to indicate that artificial immunization affords anything resembling a perfect method for combating Bang's disease, or as satisfactory in dealing with many infected herds as testing and elimination programs, we are led to suspect strongly that, by selecting *Br. abortus* strains of proper virulence for vaccine preparation and by confining the use of vaccine largely to unbred animals, possibly calves or virgin heifers at near breeding age, immunization may be perfected to the point where in many herds it may be found to serve a useful purpose in reducing abortion losses and assisting herd-owners gradually to eliminate the disease without at the same time being a menace to human health."

In a report to the U. S. Livestock Sanitary Association in 1929 (195), the writer made a statistical study of biologicals commercially available in

this country for infectious abortion. It was found that there was a wide variation in sources of cultures and in methods of manufacture of the different products. There were no reliable statistical data to prove the value of any of the products. There was no oneness of mind in respect of the desirability of using avirulent cultures for vaccines or of the danger from virulent cultures.

Torrey and Hallman (1930) (196) studied nine commercial vaccines for viability and virulence. On the basis of cultural tests, three were found non-viable and a fourth contained only a few viable bacteria. Virulence tests on guinea pigs showed that two of these four contained a few viable, virulent organisms. Of the five remaining vaccines, two appeared to be highly attenuated, but not non-virulent, and one of these appeared to be able to acquire greater virulence by animal passage. Three vaccines showed more virulence for guinea pigs than many recently isolated strains. The writer has learned privately that *Br. suis* has been found in at least one commercial vaccine. The number of bacteria per dose varied from 200 billion in one of the most highly attenuated vaccines to 1,200 billion in one of the most virulent vaccines.

Following the studies of Torrey and Hallman, both the American Veterinary Medical Association and the U. S. Livestock Sanitary Association went on record as opposed to the use of virulent live culture vaccines for Bang's disease. However, there is justification for continued work with a non-virulent live culture vaccine for this disease, and there is a great deal of weighty evidence that such a vaccine is available in the case of Huddleson's avirulent, non-agglutinogenic, live culture vaccine. Mallmann has found this organism to be an S type. Huddleson is able to keep this organism stable in its characteristics over a long period of years. There is no evidence that this organism can develop increased pathogenicity by passage through vaccinated cattle since it probably does not leave the body of the vaccinated animal. It can be isolated from the blood of the vaccinated cow for only about five days following the inoculation. The culture from which the Huddleson vaccine is made has, so far as we can ascertain, been studied for a longer period of time than any other *Brucella* culture and there have accumulated more data of a more favorable character concerning this culture than any other. The Detroit Board of Health permitted one of its certified herds to be vaccinated with the Huddleson vaccine.

As in the United States so in Europe and other countries, there has been too much indiscriminate vaccination on a large scale and too much testing of vaccines in an experimental way and too little consistent study of a given strain of *Brucella* selected with a view to its ability to conform to the theoretical requirements of an ideal culture for the production of a vaccine.

In connection with vaccination against *Brucella*, it is interesting to note the violently antagonistic attitude of the proeradicationists and anti-vaccinationists. Reference has already been made to the fact that the writer (180) took occasion to discuss the matter before the 1932 meeting of the U. S. Livestock Sanitary Association.

Pasteurization—From the public health standpoint, pending the time when Bang's disease of cattle may be considered to have been eradicated in a given area, it is recommended that all milk coming from cows that react to the agglutination test for *Brucella* or from cows of unknown status in respect of brucellosis be effectively pasteurized. The usual legal require-

ments for milk pasteurization are adequate for protection against *Brucella*, but the factor of safety is probably less than in the case of the other pathogens found in milk.

Experiments reported by Boak and Carpenter (1931) (197) indicated that the present requirements for pasteurization of milk (heating at 142-145° F. for 20-30 min.) are adequate for destroying the most virulent strains of *Br. abortus*.

Recently, Murray et al. (1932) (198) reviewed the literature on pasteurization of milk containing *Brucella* and reported on their own experiments. They used a standard pasteurizing outfit and found that a temperature of 62-63° C. (143.6-145.4° F.), applied for three minutes, is sufficient to destroy both bovine and porcine varieties of *Brucella*. Thus they concluded that the usual procedure of 62-63° C. for 30 minutes gives ample factor of safety, provided the pasteurizer is operated in the proper manner. With the lid of the pasteurizer open, viable *Brucella* were isolated even after 30 minutes. A flush gate valve is also necessary. In experiments in which an ordinary faucet outfit was used, live organisms were found after 30 minutes.

The writer (1926) (199) participated in some experiments in which both *Brucella* and *Mycobacterium tuberculosis* were tested by the Electropure process.* The following conclusions from that work indicated that *Brucella* is slightly more resistant than the tuberculosis bacillus:

1. When artificially infected milk was subjected to the ELECTROPURE treatment, with the apparatus set to operate at 150° F., the treatment was ineffective in destroying the viability of *Mycobacterium tuberculosis*, *Brucella abortus* and *Br. melitensis*.

2. When artificially inoculated milk was passed through the ELECTROPURE apparatus, set to operate at 155° F., no viable *Mycobacterium tuberculosis* were found in the treated milk, but viable *Br. abortus melitensis* were demonstrated to have been present, in three out of thirteen 3 cc. samples injected into guinea pigs.

3. When artificially inoculated milk passed through the ELECTROPURE apparatus, set to operate at 160° F., the milk was rendered free from living *Mycobacterium tuberculosis*, *Br. abortus* and *Br. melitensis*.

Park, S. E., Graham, R., Prucha, M. J., and Brannon, J. M. (1932) (200) studied pasteurization of milk artificially infected with two strains of *Brucella suis* and summarized their results as follows:

- "1. Two strains of *Brucella suis*, in hermetically sealed glass tubes of whole milk (500,000,000 organisms per cubic centimeter), were non-viable after twenty minutes at 140° F., after fifteen minutes at 142° F., and after seven minutes at 144° F.

- "2. The same strains proved more resistant to heat in cotton-stoppered tubes of milk. *Brucella suis* survived for thirty minutes at 144° F. in milk containing 10,000,000 to 500,000,000 organisms per cubic centimeter, but the same period of time at the same temperature destroyed *Brucella suis* in milk containing 5,000 to 1,000,000 organisms per cubic centimeter. Therefore, it appears that the thermal death time is influenced by the degree of contamination."

In a foreword to this paper, Andy Hall, Director of Public Health of Illinois, Chairman of the State Undulant Fever Committee, made this comment:

Undulant fever as a public health problem is unique in many ways. It has been recognized as such only recently. That the principal source of the disease is in

*For a brief description of the apparatus used see pp. 114 and 212, Giltner's Textbook of General Microbiology. Blakiston's Son and Co., 1928.

domestic stock no well informed observer doubts. There is no uniformity of opinion concerning the relative importance of channels through which the infection may reach man from animals. No student of the subject denies that infected milk may result in spreading undulant fever among humans.

A recent analysis of 155 cases of sickness that occurred during 1929 and 1930 in Illinois and which were clinically and serologically diagnosed as undulant fever cast a very strong suspicion on raw milk supplies as the agent of transmission in a significant percentage of the total incidence. Observers elsewhere have found evidence that infected milk may be an important means of transmitting the disease.

Furthermore, undulant fever prevalence may be on the up curve, potentially at least. If nothing is done to control the disease a great endemic wave of this ailment among men in the not far distant future is a catastrophe which is well within the realm of the possible. On the other hand a relatively small amount of judicious energy spent now in research and control may offset that possibility.

For these reasons, it seems of the greatest importance to bring to light all possible knowledge about the cause of undulant fever and means of controlling and spread of it. The accompanying report is a contribution to an important phase of this knowledge. Some controversy about the efficacy of pasteurization in destroying the causative organisms of undulant fever has arisen. Doubts created by this controversy will survive until the matter is settled by undisputable scientific experimentation. This report might be accepted as closing the chapter on one phase of the necessary experimentation.

Pasteurization should not be universally required for all market milk. The writer (1932) (201) has discussed this matter in a paper in defense of certified milk. Opposition was expressed to commending the pasteurization of a milk of low grade or to substituting pasteurization for more logical methods of handling infectious diseases of cattle. There is just as great a source of danger due to the shortcomings of pasteurization as there is due to the remote possibilities of pathogens in a high-grade raw milk. Commercial pasteurization has become a highly technical process the benefits of which are available only to communities of considerable size. The crude heating of milk so that it is safe so far as *Brucella* is concerned is a technic that can readily be mastered by the housewife. Under circumstances that do not clearly safeguard the health of the family it is better to boil milk before using than to use it raw.

Recently, in Health News (v. IX, No. 31) of the New York State Department of Health, there was given a letter of a mother who protested against the rescinding of a pasteurization ordinance by a village board of health.

She wrote,

"I am making this plea to save any mothers the anguish which I have just gone through and had it not been for some doctor on the job who knew his business enough to send a specimen of my little girl's blood to Albany and had it confirmed 'Undulant Fever', I think that this summer would have found one little cot at the lake empty and through no carelessness in any way on a mother's part but only through ignorance for we had not been sufficiently warned of the danger lurking in raw milk."

The report of the Committee on Milk to the Conference of State and Provincial Health Authorities (June 2, 1932) attempted to answer the question: What practical methods can be devised and recommended to increase the percentage of pasteurized milk for sale in the smaller cities and towns of the country?

The committee believes that this is a very important problem, since the milk-borne outbreak reports of the (U. S.) Public Health Service and the American Child Health Association clearly indicate that the vast majority of milk-borne outbreaks of disease occur in small communities in

connection with raw milk supplies. It is believed that the solution of this problem should be largely through educational means and that compulsory pasteurization ordinances should be passed only after the educational program has reached and convinced an unmistakable majority of the population. The local health officers of communities in which any considerable percentage of the market milk is still sold raw are urged to use an educational approach similar to that recommended in the Public Health Service Milk Sanitation Program under the chapter heading "What Policy Should the Health Officer Adopt with Reference to Pasteurization and with Reference to Increasing to the Optimum the Per Capita Consumption of Milk?" (Public Health Reports, Vol. 47, No. 33, August 12, 1932).

At the 1932 meeting of the Society of American Bacteriologists, at Ann Arbor, Gilbert and Coleman (202) made a report on their study of undulant fever in New York State. They found that over 2,000,000 people in the State have a raw milk supply. While they located several hundred cases a year in the State, they believe that only one-tenth of the cases are recognized. On this basis, there would have been several thousand cases a year in New York or more than are reported annually to the U. S. Public Health Service for the entire United States. They reported that nearly all of the New York cases are due to the bovine type of *Brucella* and that most of the cases had no contact with cattle; consequently, raw milk seemed to be the source of the trouble.

Control of Brucellosis Caused by Infected Animal Food Products Other Than Milk and Dairy Products

Very little work has been done to determine how serious a menace to health are *Brucella* infected meat and other animal products, aside from milk, or how practical control of these sources of danger may be achieved. Krueger (1932) (203) performed some experiments to determine if the Bang bacillus could live in muscular tissues of slaughtered animals for any length of time after the carcasses had been subjected to commercial refrigeration. To carry out this experiment fascia-covered muscle sections were removed and seared at both ends. Following this, the muscles were injected with large quantities of live Bang organisms which through massage were thoroughly and evenly distributed through the meat substance. The pieces of meat so inoculated were placed in a refrigerator at 3-5° C. for a period of two weeks. At first daily and later every other day deep sections were removed from these muscle samples, macerated in physiological salt solution and injected intraperitoneally into guinea pigs to determine the presence or absence of live Bang organisms. Samples taken as late as two weeks revealed virulent cultures as determined by guinea pig inoculations.

In a recent piece of work,* Huddleson, Johnson, and Hamann (1932) (204) studied a total of 3,975 hogs slaughtered at two packing houses in Michigan. By means of the whole blood rapid agglutination test they found 388 or 7.74 per cent to have agglutinins for *Brucella* in their blood. From the tissues of 41 or 13.31 per cent of the reacting hogs they recovered *Br. suis*. The maintenance of hog tissues naturally infected with *Br. suis* at a temperature of 10° F. for 30 days had little effect upon the viability of the organism. When hog spleens naturally infected with *Br. suis* were kept in meat curing brine for as short a period as five days it was very difficult

*Partly financed by a grant from the Scientific Committee of the Am. Med. Ass'n, and the Commonwealth Fund.

to recover the organism by cultural means, but it could be recovered in small numbers in heavily infected spleens after a sojourn in brine for forty days.

The data from the examination of 167 employees in packing houses indicated that 10.7 per cent according to the agglutination test or 23.9 per cent according to the opsonocytophagic activity test had been exposed to *Brucella* presumably as a result of handling infected hog tissues.* The results from retesting 18 employees in one packing house after the occurrence of a definite clinical case of undulant fever indicated that when exposure to infective material takes place the exposed individual develops either active immunity or active infection.

There is no experience to which we can refer for a practicable solution for the problem of brucellosis acquired by contact with meat and other animal products. It is inevitable and probably desirable that animals infected with such diseases as tuberculosis and brucellosis be slaughtered in a packing house. It should be required that this be permitted only on condition that there be in force an adequate inspection service. Approximately 70 per cent of the meat food animals slaughtered in the United States are slaughtered in establishments which are under federal inspection. A small percentage of the remainder is subjected to state or municipal inspection which is in some cases comparable in adequacy to the federal inspection and in many cases wholly inadequate. A competent veterinary pathologist can readily detect tuberculosis in most infected carcasses, but the lesions of brucellosis, especially of hogs, are not so conspicuous or characteristic that they may serve as a basis for condemnation of the carcass. This subject is now under study. It appears that the packing house employee must accept brucellosis as an industrial hazard and protect himself as best he may by avoiding skin injuries, proper care of those that occur, and by precautions against the ingestion of raw meat food products. The employer probably must squarely face brucellosis as a compensable disease.

The approach to the swine brucellosis problem by an attack on the disease at the farm does not offer immediate hopeful promises of success. The limitations of the agglutination test are not yet known, and it is the only available diagnostic test at the present time. This is a problem that must receive the attention of the practicing veterinarian and of the swine raiser. The public health officer must have a full realization of the fact that *Br. suis* is more pathogenic for man than is *Br. abortus* and that it is probably as serious a menace to man as is *Br. melitensis*.

Epidemiological evidence is accumulating to arouse the suspicion that some of the cases of brucellosis encountered in this country are not traceable to caprine, bovine or porcine sources. Whether poultry or eggs constitute a menace to man has not been proved, but they are under suspicion, the former through handling in preparation for cooking and the latter because of the fact that cooking ordinarily does not sterilize eggs.

The Problem of Infection Through Contact with the Living Infected Animal—Veterinarians, livestock men and all others who come in contact with cattle should be taught to appreciate the danger that lies in bovine infectious abortion or Bang's disease. In the past there has been an utter lack of regard for the direct communicability of *Brucella* infection from the infected cow to man. At present there are those who would minimize the importance of consuming infective dairy products and magnify the importance of animal contacts. There is nothing to be gained by taking either stand. It is epidemiologically established that dairy products may be in-

fective and it is clinical experience that intimate contact with infected cattle may result in some manifestation of brucellosis in man. Consequently, those who must make contacts with infected cattle should exercise reasonable precautions with respect to disinfection especially in connection with the handling of abortions and parturitions. The veterinarian should not only protect himself, but it should be his duty to warn his clients of the dangers involved and either instruct them how to protect themselves or advise them to consult their family physician. It is highly important that physicians, especially those engaged in country practice, acquaint themselves with the subject of brucellosis so that an accurate diagnosis shall be made in these animal contact cases, and so that proper treatment shall be administered. It may become necessary to advise vaccination to veterinarians.

The problem of the infected goat is one that need not be allowed to develop in the United States. In Mediterranean countries it is so serious that human vaccination with living avirulent culture may be necessary to supplement ordinary hygienic precautions. Brucellosis of sheep may develop into a human contact infection problem where *melitensis* infection is common, but it would present no special problems for solution. Veterinarians and sheep breeders and feeders should be warned.

It has long been known that the horse tribe is susceptible to *Brucella* and it is to be expected that man may acquire the infection from affected equidae. Kennedy (19) (see page 11) noted that mules were susceptible to *Br. melitensis* and Fitch, Bishop and Boyd (1932) (205) gave a number of references to the literature concerning equine brucellosis. Probably, all three species of *Brucella* produce local infections, poll-evil, fistulous withers and other forms of cellulitis, in the horse and mule. What has been stated relative to guarding against human brucellosis of bovine origin applies in this connection. The danger is less because of the relatively small number of cases involved and, because of the nature of the equine disease, there is less opportunity for human contact with infective material. It is of interest that farm horses have been shown to have agglutinins for *Brucella* to a considerable degree, while city or army horses react negatively to the agglutination test.

It is especially important that veterinarians and swine breeders and feeders take precautions against *Br. suis* infection. The *Brucella* that infects swine is far more virulent than is *Br. abortus*. Again, the measures already indicated should be taken to prevent this infection from occurring in man or correctly to diagnose and treat it when it occurs.

The British Commission (206) studied the possibility of infection from *melitensis* in rats, dogs, and cats. Dogs and cats were found to be naturally infected and were considered possible sources of infection to man. Aubert, Cantaloube, and Thibault (1910) (207) found in the Department du Gard, France (Mediterranean littoral) 29.77 per cent of the goats examined reacting to the agglutination test, 9.33 per cent of the sheep and 21.68 per cent of the rabbits. One cat of 13 examined reacted as did one guinea pig of four examined. (The guinea pig is, of course, very susceptible to *Brucella*). None of the horse tribe, swine or dogs examined gave a positive reaction. Infection in the dog is known to occur in the United States. Our attention has been called to a dairy barn cat whose blood reacted to the agglutination test for *Brucella*. These facts may help to explain certain cases of brucellosis of obscure origin, but they have little bearing on the major aspects of the problem.

Laboratory Infections

Finally, it is notable that many laboratory workers become infected with *Brucella*. The experience of our own laboratory may be more extraordinary than typical but, if so, it is probably because of the extent of the work and peculiar nature of some of the projects. Certainly, it is our experience that many students and nearly all new workers, janitors, dish-washers, technicians, and research workers, who identify themselves with the *Brucella* projects become infected. Occasionally, workers in the laboratory engaged in work which has not been in any way related to *Brucella* cultures or to *Brucella* infected tissues have become infected. The severity of the infection has varied from a protracted and grave illness necessitating hospitalization for many months to a slight indisposition or a reaction that has manifested itself only by the appearance of agglutinins in the blood, a skin sensitization or an increase in the opsonocytophagic power of the polymorphonuclear leucocytes or perhaps only one or a combination of these reactions. Brucellosis may not be so readily contracted in the laboratory as is tularemia or psittacosis but it is a common laboratory infection. This may be due to the fact that carelessness prevails in the handling of cultures and infective materials, a carelessness begotten of general ignorance of or indifference to the susceptibility of man to each of the species of *Brucella*. There is, in addition, the fact that within recent years a great many persons have been employed in research projects or routine procedures related to brucellosis.

Laboratory infection of man should be combated by the adoption of a different attitude toward brucellosis and a better technic in regard to manipulation of cultures and infective material of all kinds. Certainly the laboratory cases are more apt to be diagnosed early and correctly and to receive the most scientific care. The writer is not inclined to dignify these cases by designating them "martyrs to science"; they may be martyrs to carelessness and poor technic. Most of these cases could be avoided. This discussion suggests the question "How resistant is *Brucella* to physical agents?" The British Commission did a great deal of work on this subject as have others. Since the microbe is not a spore producer and since it has no other special protective chemical or physical properties, its resistance to chemical disinfectants is comparable to that of the typhoid bacillus. The recent experiments of Cameron (1932) (208) conducted to determine the duration of viability of *Br. abortus* (and *Br. suis*) showed that the organisms lived:

1. Four and a half hours when exposed to direct sunlight.
2. Five days when dried in burlap sacking kept on a laboratory table.
3. Thirty days when dried in burlap sacking kept in an unheated cellar.
4. One hundred twenty-one days, the maximum interval covered, when dried in the presence of nutrient materials.
5. Seventy-two days when dried in the absence of nutrient material.
6. Less than four days in soil which dried quickly in Petri dishes placed in an unheated cellar during October.
7. Twenty-seven days, the maximum interval covered, in soil treated in the same manner as in the preceding experiment, but conducted during February.
8. Thirty-seven days in soil that dried slowly in test tubes kept in a laboratory cupboard.
9. Sixty-six days, the maximum interval covered, after having been in wet soil stored in an unheated cellar.
10. Four days in normal bovine urine at room temperature.

11. One hundred twenty days in bovine feces kept in test tubes in a laboratory cupboard and dried very slowly.
12. One hundred days in bovine feces which were kept in an unheated cellar and did not dry.
13. Seventy-seven days, the maximum interval covered, in the presence of putrefaction.
14. Seventy-seven days in tap water which was sterilized before the organism was introduced and kept at room temperature.
15. One hundred fourteen days in tap water kept at a temperature approximating -4° C.

V. SUMMARY

Brucellosis is primarily a disease of the lower animals communicable to man by contact or by the ingestion of infective material but probably never or rarely communicated from man to man. The disease under many different names has been known for centuries but had not been at all well understood until less than half a century ago when the causative agent of Malta or undulant fever was isolated by Bruce. The discovery that the goat is the reservoir of the microbe of Bruce seemed to offer a solution for the problem of undulant fever as it manifested itself in Malta and the Mediterranean countries, geographical sections that had in the past furnished various names for this peculiar fever. However, the disease proved not easily conquered due to difficulties in diagnosis, greater difficulties in controlling the sources of infection and seemingly insuperable difficulties in therapeutics. Within more recent years, the situation became complicated by the discovery of Evans that the Bang bacillus of bovine infectious abortion is closely related to the microbe of Bruce. The cattle disease in the meantime has extended to all countries and has each year infected larger numbers of herds and individual cattle. The discovery that the bacillus of Bang is excreted in the milk seemed to offer a satisfactory explanation of the brucellosis of man in those parts of the United States and other countries that do not have a large milch goat industry. But it was soon evident that this was not an adequate explanation of all such cases.

Not many years after the discovery of the Bang bacillus, swine were found to be not infrequently affected with a species of *Brucella* that differed somewhat from the Bang bacillus. Cattle were found to be at least slightly susceptible to the *Brucella* from swine but swine were not found susceptible to the Bang bacillus. Sheep, horses, mules, dogs, cats, rabbits, and domestic birds as well as many wild mammals were found to acquire brucellosis sometimes obviously from contact with infected cattle, goats or swine, and sometimes from contacts of unknown or unsuspected nature.

Huddleson determined that there are at least three species of *Brucella* with a primary host for each, *Br. abortus* of the cow, *Br. melitensis* of the goat, and *Br. suis* of the pig. Each of these species may infect various other animals, but each is most frequently found in its own primary host and is usually but not invariably the etiological factor in the peculiar brucellosis of that species. Man has been found to be susceptible to all three species. *Melitensis* and *suis* are more virulent to man than is *abortus*.

Melitensis infection is most common in regions where the milch goat is the main source of milk and its products. Man acquires the disease from ingestion of goat milk and its products and from contact with affected goats or goat tissues or excretions. In these sections, *melitensis* infection spreads to sheep and cattle and other animals and from them to man.

Abortus infection is most common in countries where there is a highly developed dairy cattle industry especially if there has been considerable traffic in European and American (United States) bred cattle. It is transmitted to man by ingestion of raw milk and its products and by intimate contacts with cattle, especially such contacts as are peculiar to veterinary practice.

Suis infection is confined for the present almost exclusively to the hog raising sections of the United States, although it has extended to other parts of the United States and to other countries. Man acquires the disease by contacts, especially in the hog packing plants, in the butcher shop, and on the farm or as a result of handling or eating unsterilized infective pork. It has been found in man as a result of infection from bovine sources since cattle occasionally acquire *suis* infection.

Human infection from other animals, horse, mule, rabbit, and poultry, is believed to be not only possible but actually the explanation of some of those cases that do not seem to be traceable to goats or sheep, cattle, and swine.

Laboratory infection from each of the three species of *Brucella* is common, *suis* or *melitensis* being usually responsible for the infection.

Huddleson and his associates have made diagnosis a practicable procedure so far as the lower animals are concerned by developing the rapid plate method for the agglutination test for either blood or milk. They have also developed a satisfactory skin sensitization reagent and an opsonocytophagic test to supplement the agglutination test and blood and urine culture in the diagnosis of human infection. They have made primary cultivation of the species of *Brucella*, especially *abortus*, comparatively certain by the introduction of liver infusion media, bacteriostatic dyes, and the use of a limited CO₂ atmosphere.

The specific therapeutics of brucellosis has been consistently unsatisfactory until the present time. Huddleson and Johnson (1933) (209) have produced a culture filtrate which has proved reasonably safe and effective in a considerable series of cases in humans of all ages and both sexes due to each of the species of *Brucella*. With a combination of diagnostic tests they have been able to determine the status of the individual with respect to susceptibility, infection, progress of the disease, and subsequent immunity with its peculiar sensitization to *Brucella* protein.

The prevention of brucellosis in man is essentially a problem in animal hygiene. The incidence of the disease in man indicates that it is, as regards a large block of cases, an industrial disease occurring more frequently in males than in females and in the age group of the industrial worker. Both sexes regardless of occupation include many individuals who are constantly or occasionally exposed to one or more sources of infection and some of whom are susceptible and contract the disease. Attempts are being made to eradicate brucellosis of cattle, Bang's disease or infectious abortion, by blood testing (agglutination test) and isolation or disposal of all reactors, disinfection of the premises and replenishing the herd with non-reactors only or by building up the herd from its own progeny, as far as possible. This program has been attended with favorable results in many herds but not in others. It has been applied to only an insignificant percentage of the total herds of this country. While experience with bovine tuberculosis, a disease presenting many analogies to brucellosis, indicates that governmental financial aid and coercion make possible the eradication (or, more correctly, the reduction of the infection to a very low percentage)

of a cattle disease over considerable areas, still it is not considered wise at this time to undertake any such program with brucellosis of cattle, goats or swine. At the same time it is not good economics to depend upon a dangerous communicable disease to serve as an agent in controlling the supply of agricultural products such as cattle, calves or milk.

Vaccination of cattle and goats by the use of an avirulent, non-agglutino-genic, live culture vaccine of *Br. abortus* is considered feasible. It may be used to supplement the plan of testing and segregation especially in herds where the plan is not workable and especially under circumstances where there is not an excess of cattle for the needs of the people.

No plan has been advanced for coping with the swine brucellosis problem. It is reasonable to expect that it will not solve itself spontaneously. Further serum agglutination tests of swine on farms and in the packing houses are advised in order that a better estimate of the extent of the disease may be attained. Veterinary practitioners and meat inspectors should be made the instruments through which a better conception of the brucellosis problem may evolve and an immediate attack against the disease may be instituted. It would be desirable but practically impossible to locate every focus of swine brucellosis and proceed accordingly to protect the owner, the swine industry, the pork packer and butcher, and the public. But the veterinarian can locate many of these foci and the pork packer's establishment could be made the medium whereby many cases could be traced back to specific farms.

The general public can be given a considerable degree of protection by legally enforced and voluntary pasteurization of market milk and milk to be used for dairy manufactures. The pasteurization must be rigidly controlled and maintained at the required standard. The factor of safety is necessarily small since the effective thermal death point of *Brucella* in milk under the conditions of commercial pasteurization is very close to the temperature at which cream line and taste are adversely affected. Local ordinances and enforcement will be more effective than state or national measures. An educational campaign designed to prepare producers, consumers, and health enforcement officers should pave the way for legal measures. It is not commercially feasible at the present time to install pasteurization equipment in all rural communities. Consequently, resort must be had to domestic pasteurization of milk from questionable sources. Milk can be heated in any household so that the danger of its transmitting *Brucella* can be eliminated. It is urgent that those who depend upon certified milk or grade A raw milk shall satisfy themselves of the safety of their milk supply with respect to *Brucella* or effectively heat all such milk before using it.

There is sufficient evidence so far as brucellosis is concerned to warrant issuing a warning against the consumption of pork and pork products unless they are thoroughly cooked. There are other diseases such as trichinosis and measles (tapeworm) conveyed to man by pork and not necessarily eliminated by meat inspection so that brucellosis constitutes only an additional reason for eating only thoroughly cooked pork.

Finally, brucellosis should not be given a rating as a public health problem out of proportion to its real importance, nor should it be neglected or minimized. On the contrary, brucellosis should be watched with grave concern by the public health official since it may well be a "disease of the future". It should receive careful study by the medical practitioner both with respect to its clinical manifestation and to laboratory diagnostic aids.

It should not be neglected by the investigator since the scientific facts already available concerning *Brucella* and brucellosis are at the most only a good foundation on which to build a structure of fuller understanding of the microbes and the diseases which it is capable of causing.

VI. CONCLUSIONS

1. Brucellosis is a public health problem of considerable proportions and one that is becoming more serious. It has spread all over the civilized world and affects persons of all ages and both sexes regardless of occupation. However, brucellosis is conspicuously an industrial disease affecting the industrial age group, especially males.
2. Brucellosis is a disease communicable to man from the lower animals by direct or indirect contacts or by ingestion of infective animal products. The goat, cow and pig seem to be the primary hosts of the three species of *Brucella*, *melitensis*, *abortus* and *suis* respectively. The sheep, horse, mule, rabbit and domestic fowl not infrequently contract the disease. Other domestic as well as wild mammals and birds are known to be susceptible to the different species of *Brucella*, and when they acquire the disease they may be the source of infection for man.
3. The diagnosis of brucellosis can be made with reasonable accuracy by means of clinical and epidemiological study supplemented by the agglutination test, and in human cases by blood and other cultures, the skin sensitization test, and the opsonocytophagic determination.
4. There has appeared no successful specific or non-specific therapeutic agent for brucellosis unless it be the culture filtrate now under investigation by Huddleson and his associates for human cases.
5. The control of brucellosis is a problem in animal hygiene. The animal sources of infection must be brought under control. Some modification of the "area plan", which has met with considerable success in the eradication of bovine tuberculosis, may prove to be of value in the eradication of Bang's disease, bovine brucellosis or infectious abortion, and perhaps of brucellosis of swine and other animals. Vaccination may be a *dernier ressort* both in the case of man and the lower animals.
6. Pending the achievement of a brucellosis free animal population or an acceptable immunizing agent, man must seek protection from brucellosis through pasteurization of milk, thorough cooking of meat, and the adoption of a judicious technic with respect to necessary contacts with animals and animal products.
7. Many important facts have been more or less firmly established concerning *Brucella* and brucellosis, both scientific and practical; but it is recognized that laboratory, clinical, and epidemiological studies of *Brucella* infections must be pursued further if these infections are to be successfully combated.

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460 B. C.-1897 A. D.

Hughes (1) (1897, page 29-34), to quote Eyre (see below) "included a comprehensive bibliography of Mediterranean Fever, ranging in point of time from the Epidemics of Hippocrates (460 to 357 B. C.) to the date of publication," 1897. "In the compilation of his list—a work in which he had the advantage of Professor Zammit's assistance—Hughes searched through rare and some unique volumes, both in manuscript and in type, lodged in the Bibliotheca of Valetta, and so secured many valuable references not elsewhere obtainable."

After the reference to Hippocrates, Hughes' next reference is 1709, Bates, 7, Naval Surgeon. An enchiridion of fevers incident to seamen in the Mediterranean, 2nd, ed., London. A bare half-dozen references to the literature are attributed to the 18th century. From 1800 till the middle of the nineteenth century only a few over a dozen references could be found. From then on until 1897, the literature is rich in references to many aspects of the disease.

1897-1907

In the Report of the British Mediterranean Fever Commission, Part V., (pp. 67-75), Eyre presented a chronological list which is a continuation of Hughes' bibliography, and embraces the period from 1897 to January, 1907. Eyre also (pp. 76-87) arranged his references by authors, alphabetically. While 112 authors are cited, 211 titles are listed, since some of the authors are credited with a considerable number of titles: Bruce, David, British, 6 titles; Craig, C. F., and Curry, J. J., Americans, 2 each; Dalton, F. J. A., British, 4; Eyre, J. W. H., and Gilmour, R. T., British, 5 each; Hayat, I. E., French, 2; Horrocks, W. H., and Kennedy, J. C., British, 10 and 13; Nicolle, C. H., French (Tunis), 6; Ross, E. H., British, 8; Shaw, E. A., and Smith, P. W. Bassett, British, 13 and 14; Wright, A. E., British, 4; and Zammit, Maltese, 6.

1903-1932

The writer has canvassed the Index Medicus and the Quarterly Cumulative Index Medicus from 1903 to date in an effort to study the development of investigations into undulant fever and cognate subjects with the following results:

Year	Malta Fever References	Eyre's List	Year	Malta Fever References	Year	Malta Fever References
1903.....	11	21	1908.....	46	1914.....	48
1904.....	16	16	1909.....	43	1915.....	19
1905.....	31	49	1910.....	79	1916.....	13
1906.....	40	47	1911.....	73	1917.....	9
1907.....	35	5	1912.....	48	1918.....	12
			1913.....	47	1919.....	10

Year	Malta Fever	Infectious Abortion	Abortus and Melitensis	Total
1920.....	12			12
1921.....	12	25		37
1922.....	16	29		45
1923.....	18	27		45
1924.....	33	29		62
1925.....	33	40		73
1926.....	46	40	6	92
1927.....	64	24	36	124
1928.....	69	29	42	140
1929.....	197	30	40	267
1930.....	207	33	45	285
1931.....	193	32	43	268
1932--Part of.....	78	7	17	

Except for the decided slump during the world war period, there has been a steady increase in the output of literature on Brucella and brucellosis during the past three decades. Beginning with 1921 for a period of five years the references to abortus outnumbered the references to Malta fever.

Year	Malta fever	Diagnosis	Experimental	Immunity	Therapy	Complications and sequelae	Epidemiology and statistics	Prevention	Transmission	Blood in	Pathology and pathogenesis	In animals	Pathology	Vaccines	Antiserum	History	Mortality	Abortus and melitense group	Infectious abortion	Totals
1927.....	29	10	2	4	7	4	6	1	1	—	—	—	—	—	—	—	—	36	24	124
1928.....	38	11	—	3	8	4	2	—	—	3	—	—	—	—	—	—	—	42	29	140
1929.....	116	14	1	5	21	11	18	1	—	2	4	4	—	—	—	—	—	40	30	267
1930.....	111	21	—	1	13	15	13	1	—	2	4	18	1	2	1	—	—	45	33	281
1931.....	90	26	1	5	11	13	12	2	9	1	4	16	2	—	—	1	—	43	32	268
1932.....	30	8	2	2	5	13	6	2	2	—	1	4	—	—	—	2	1	—	—	In-complete

In 1927, Quarterly Cumulative Index Medicus began to subdivide the references under Malta or Undulant fever using the topics in the headings of the columns in the above table. In the five year period 1927-1931, the total number of references more than doubled and the references to infectious abortion and the abortus-melitensis group steadily increased.

**BIBLIOGRAPHIES ON BOVINE INFECTIOUS ABORTION
PREPARED BY THE WRITER**

For the period up to and including 1917 we listed 154 references on page 26 of the 21st Annual Report of the United States Livestock Sanitary Association :

- for 1918, 21 references on p. 150 of the 22nd Annual Report,
- for 1919, 36 references on p. 123 of the 23rd Annual Report,
- for 1920, 52 references on p. 96 of the 24th Annual Report,
- for 1921, 44 references on p. 48 of the 25th Annual Report.

Since 1921 the Journal of the A. V. M. A. has printed the bibliographies as follows :

- for 1922, 54 references, p. 398, lxiv, December, 1923,
- for 1923, 76 references, p. 532, lxvi, January, 1925,
- for 1924, 57 references, p. 238, lxviii, November, 1925,
- for 1925, 96 references, p. 393, lxx, December, 1926,
- for 1926, 96 references, p. 114, lxxii, October, 1927,
- for 1927, 85 references, p. 232, lxxv, August, 1929,
- for 1928, 152 references in mimeographed form only.

